Cortone

TRADE MARK

A HANDBOOK OF THERAPY

Published by

MERCK (NORTH AMERICA) INC.

161 Avenue of the Americas, New York 13, N Y , U S.A.

Export Subsidiary of MERCK & CO , INC —RAHWAY, N J.

In Canada MERCK & CO LIMITED—MONTREAL

Foreword

This *Handbook* is designed as a convenient aid in the daily practice of medicine. It supplies up-to-date information on the use of cortisone, based on the clinical experience of many authorities.

Part I presents ready reference to therapeutic agents and procedures generally used in the treatment of diseases for which cortisone is indicated. Pertinent information on the use of cortisone has been included to show the integral place of this hormone in the pattern of modern therapy.

Part II supplies concise information on the clinical use of CORTONE Acetate and HYDROCORTONE Acetate. Recommended dosage, and the response that may be expected, are outlined in chapters devoted to individual diseases. Numerous representative case histories and clinical photographs provide graphic "yardsticks" by which the physician may measure the progress of his own patients.

Part III reviews the development of cortisone research and the physiologic considerations that form the background of cortisone therapy.

Because of its ability to suppress active disease manifestations, cortisone is especially valuable in the earlier stages of disease. Therefore, the family physician—through early diagnosis—has the greatest opportunity to utilize this important therapeutic agent with optimal benefit to his patients.

CONTENTS

PART I

PART II

Treatment with CORTONE

LIST OF ILLUSTRATIONS

Essentials of Modern Therapy

THE PLACE OF CORTISONE IN THE PATTERN OF TREATMENT

Rheumatoid Arthritis

Over the years, many forms of therapy have been suggested for rheumatoid arthritis. These have included general measures such as rest, physiotherapy, more adequate nutrition, and a great number of medicinal preparations. Of the latter, salicylates, gold compounds, foreign proteins, vaccines, and massive doses of vitamin D have been most widely employed. At present, only salicylates and gold compounds are most generally used.

Salicylates are effective analgesics and frequently are given to tolerance. Gold compounds produce remissions in many patients with active rheumatoid arthritis, but toxic reactions are not uncommon, and chrysotherapy is contraindicated in the elderly or in patients with a history of hepatic or renal damage or blood dyscrasia.

Investigation of the adrenal cortex finally yielded the clue to a new agent—cortisone—the antiarthritic effect of which proved to be unequalled by any drug previously available. In contrast to the results obtained with the older drugs, cortisone almost invariably produces some degree of relief, and usually a striking response. A detailed descrip-

tion of the use of cortisone in the treatment of rheumatoid arthritis is presented on page 22.

Relief of subjective stiffness generally is noticeable twenty-four to forty-eight hours after the initial dose of cortisone, and sometimes as early as six hours This is followed by a decrease in articular tenderness and reduced pain on motion. Swellings of the joints diminish. There is an increase in muscle strength, and joint function may return within a few days The extent of improvement is dependent on the degree of irreversible pathologic change present. Concomitantly, the patient exhibits increased appetite, strength, and sense of well-being

OTHER MEASURES

Certain general measures are of recognized benefit in the adjunctive care of rheumatoid arthritis patients who are being treated with cortisone. These measures include rest, dietary supplementation, guided exercise, and physical therapy.

An optimistic attitude on the part of the physician is essential, every effort should be made to free the patient from anything producing anxiety or nervous strain.

It is highly important that the patient avoid overfatigue when the disease process is particularly acute, hence bed rest may be necessary. Excessive use of involved joints also should be avoided Proper posture of the patient, while in bed, should be stressed. If joints must become ankylosed, [illegible] become incapable of bearing weight.

As a rule, arthritic patients are poorly nourished and should be given a highly nutritious, balanced diet. High protein supplements such as eggs and milk once or twice a day may be added.

Physical Medicine and Cortisone: The inclusion of an

appropriate course of physical therapy in the patient's regimen frequently is of value. Very often the response to a combination of cortisone and physical therapy will be greater than that to either agent alone. Cortisone often permits the use of more vigorous and active measures, with greater comfort and effectiveness.

One highly successful program, combining physical medicine with cortisone, consists of daily systemic heating for thirty minutes in a hot tub-bath with a water temperature of 102–104° F., or in a hot moist-air "fever cabinet" raising the patient's oral temperature to 100–101° F. The application of heat is followed by light-to-deep stroking and kneading massage of the affected extremities. Active and assistive exercises are employed in an attempt to increase the range of motion. When indicated, resistive exercises are prescribed to increase muscular strength. Gait training is an essential part of the exercise program of many patients. They are taught to eliminate a limp, how to get in and out of chairs, how to use crutches or canes properly, and how to determine the tolerable amount of walking or other activity. (*See* page 37 *Martin, Polley, and Anderson.*)

Juvenile Rheumatoid Arthritis (Still's Disease)

Treatment is essentially the same as in rheumatoid arthritis in adults Juvenile rheumatoid arthritis is a modified form of the disease in that it occurs in growing joints with resultant changes in growth and development. Therefore, the prevention of deformities is especially important This disease is severe and often characterized by pronounced constitutional signs.

Rheumatoid Spondylitis (Marie-Strümpell Disease)

Cortisone, used alone or combined with conventional therapy, produces remissions of symptoms in many cases of rheumatoid spondylitis.

The conventional method of therapy has been X-radiation of the involved area and measures to prevent permanent deformity of the spine. The earlier in the disease process such treatment is instituted, the better the prognosis. When X-ray therapy is combined with postural exercise and the use of a back support, such as a Taylor brace, pain may be minimized and function preserved in many patients. Relapses often respond to further roentgen therapy. Salicylates are useful to help alleviate pain.

Peripheral joint involvement in a few patients with spondylitis has responded to gold therapy. However, gold does not have a favorable effect on the spondylitis itself and should not be used in ankylosing spondylitis.

Psoriatic Arthritis

Psoriatic arthritis has been less responsive to traditional methods of therapy than other types of arthritis, but the outlook for patients with this condition is more encouraging since the advent of cortisone. In many cases, the arthritis will respond to hormonal therapy even though skin lesions may not improve on the dosage employed.

Osteoarthritis

Local injection of *hydrocortisone acetate* has elicited striking response in many patients with osteoarthritis. (*See* page 38.) In all 39 of one series of patients, this hormone produced prompt alleviation of symptoms and signs in the joints treated, the duration of benefit from each injection varied from a few days to several weeks, repeated injections were equally effective.

Weight reduction, small doses of salicylates, simple supports, and home physiotherapy are helpful additional measures in the treatment of osteoarthritis. If joint changes already have reached an advanced stage at the initiation

of treatment, surgical intervention may represent the only way to help the patient.

Acute Rheumatic Fever

Cortisone produces striking and prompt clinical improvement in the systemic manifestations of acute rheumatic fever, *e.g.*, polyarthritis, fever, tachycardia, "toxicity," anorexia, and anemia. In some cases, cortisone may be lifesaving The abnormal laboratory features such as elevated ESR, plasma fibrinogen, serum globulin and gamma globulin, and "C" reactive protein are frequently restored toward or to normal within a few weeks. To be most effective, cortisone should be given early and in adequate amounts. Therapy should be maintained in accordance with the recommendations on page 49 until it can be established by clinical observations and laboratory tests that the acute phase of rheumatic fever has run its course and *the patient is out of immediate danger.*

OTHER MEASURES

At onset of symptoms suggesting rheumatic fever, complete bed rest must be instituted and maintained until all clinical and laboratory evidence of disease activity has subsided. A diet adequate in calories should be given. Liquid and soft diets are preferable in the early stages, especially if constitutional symptoms are present. Protein concentrates may be used; adequate fluids should be given, avoiding those which promote distention. Salt intake need not be limited, unless cardiac insufficiency is present or imminent.

In many cases of rheumatic fever the effectiveness of cortisone therapy will be enhanced by concomitant use of other drugs. Salicylates are of definite value, but are more useful in the symptomatic treatment of acute attacks than in subacute or polycyclic forms of the disease. When used in mild or moderately severe cases, salicylate therapy

should be maintained for at least two or three weeks after symptoms have subsided. After laboratory evidence of rheumatic activity diminishes or disappears, salicylates are to be withdrawn; they should be resumed if fever or joint symptoms recur. Generally, signs of rheumatic activity disappear after one to three months, but it may be six months or a year before the active disease subsides.

Digitalis should be used only when cardiac insufficiency is evident. In cardiac failure, judicious use of diuretics [illegible]

Bronchial Asthma

Adequate dosage of cortisone has produced striking results in the treatment of severe asthma, even in patients with severe chronic intractable asthma that has become resistant to other forms of therapy. The use of the hormone has been recommended also in status asthmaticus for both children and adults. (*See* page 51.)

During therapy with cortisone, the use of antibiotics and other appropriate measures for intercurrent infections is essential. Conventional antiasthmatic therapy should be used until the effect of the hormone becomes established

OTHER MEASURES

Ephedrine is effective in relatively mild attacks, and often is combined with a mild sedative, especially at night Epinephrine is indicated for severe attacks, but should be administered with caution in patients with severe hypertension, hyperthyroidism, heart disease, or sensitivity to epinephrine. Aminophylline frequently is effective in attacks that do not respond to epinephrine. Aminophylline alone or combined with ephedrine and a sedative may be useful in mild asthma.

Oxygen or an oxygen-helium mixture has proved helpful, sometimes lifesaving, but usually is not advisable unless some degree of cyanosis calls for relief. Positive pressure inhalation therapy may be advantageous to dilate the bronchi. To control excessive coughing, codeine is useful. Expectorants also are indicated, especially if given with a sedative. Ether in oil by rectum, or paraldehyde may be beneficial.

When *extrinsic allergens* are of etiologic importance in asthma, they should be avoided, if feasible, or specific hyposensitization should be attempted. Treatment with antihistaminic drugs has been successful in some cases.

Infective asthma is treated by appropriate antibacterial measures. Broad-spectrum antibiotic therapy may be instituted pending isolation and identification of the causative organism More specific antibacterial therapy may then be used. When infective asthma is associated with paranasal sinusitis, local treatment of the sinuses is essential. When the disease is associated with chronically infected sinuses, tonsils, and adenoids, tonsillectomy and adenoidectomy may be of value. Vaccines are worthy of trial in the treatment of chronic infective asthma One suggested procedure is to use a combination of autogenous and stock vaccines.

General health should be maintained, and adequate rest and nutrition are essential Suitable breathing exercises are of value in children and young adults. During acute attacks or prolonged status asthmaticus, food should be light and easily digestible Exposure to nonspecific irritants such as smoke and dust should be avoided at all times Patients may find relief in warm, dry regions.

Patients should realize that asthma is chronic and recurrent, though seldom fatal, and that prolonged treatment is necessary. Even under the most careful management, occasional attacks may occur but should not be considered evidence of failure of the antiasthmatic regimen.

Serum Sickness

Urticaria, arthralgia, and fever—the most common manifestations of serum sickness—respond promptly to treatment with cortisone. Therapeutically, it is of special significance that cortisone is equally effective in treating the *serum-sicknesslike reactions* that frequently occur after administration of antibiotics. To control itching, the following agents may be used concomitantly: antihistaminic drugs; ephedrine, epinephrine, or calcium gluconate; antipruritic lotions; and colloid baths Procaine, intravenously, may be used to relieve itching and arthralgia, and salicylates often ease the articular pains.

Inflammatory Eye Diseases

Parenteral use or topical administration of cortisone dramatically controls the inflammatory and exudative phases of certain conditions of the eye, particularly those affecting the cornea, uveal tract, and external structures of the eye. Moreover, cortisone therapy may reduce the damaging sequelae of these diseases—such as corneal scarring and vascularization—and thus prevent partial or complete blindness in many instances. Even in patients not threatened with blindness, cortisone can prevent prolonged periods of disability and acute discomfort, thus enabling many patients to pursue their daily activities. Furthermore, cases resistant to other methods of therapy frequently improve promptly after treatment with the hormone (*See* TABLE, ADMINISTRATION OF CORTONE IN VARIOUS EYE DISEASES, page 66.)

OTHER MEASURES

Adjunctive measures frequently are of great help in maintaining a favorable course. Antimicrobial therapy, when indicated, should be employed together with cortisone.

In *deep keratitis*, atropine has been used successfully to

relieve pain, and a patch applied to keep the eye at rest. *Acne rosacea keratitis* has been treated with oral doses of riboflavin with excellent results.

Allergic conjunctivitis. Removal from exposure to the causative irritant is of primary importance. When itching is intense, ice compresses or solutions containing a suitable local anesthetic may be employed.

Phlyctenular keratoconjunctivitis. In uncomplicated cases cure is usually effected by dusting powdered calomel into the conjunctival sac once a day, or by applying yellow oxide of mercury ointment to the lesions If the cornea is involved, atropine and sulfonamide drops should be used to dilate pupils and prevent secondary infection. A local anesthetic combined with epinephrine as an ointment may be used to relieve pain and blepharospasm. Dark glasses should be worn. Infective foci should be removed, and errors in diet and hygiene should be corrected. A course of tuberculin or typhoid vaccine may be tried in refractory cases.

Vernal conjunctivitis. If a causative allergen can be identified, desensitization and other appropriate antiallergic therapy are indicated The thick secretion should be washed out frequently with 3 per cent sodium bicarbonate solution. Itching may be relieved by ice compresses and the cautious use of a local anesthetic combined with epinephrine in solution during the day, and an ointment of similar composition at night. In refractory cases, radium or solid carbon dioxide may be applied to the granulations, but this procedure should be attempted only by individuals skilled in the use of these agents.

Ophthalmic herpes zoster sometimes is accompanied by multiple eye involvements including deep keratitis, iritis, and the like, and in severe cases may culminate in blindness or greatly reduced vision. The use of a collyrium, castor oil instillations, atropine, and a protective pad are indicated.

Iritis and Iridocyclitis. The patient should be put to bed in a room with subdued light. Pain may be relieved with codeine and acetylsalicylic acid. Vigorous local treatment should be begun immediately to prevent formation of posterior synechiae and to put the iris and ciliary body at rest. Atropine, every two hours until the pupil is dilated and three or four times a day thereafter, usually will maintain adequate dilatation For children, an atropine ointment is advisable. If adhesions have formed, the action of atropine may be augmented by instilling drops of epinephrine or cocaine. Subconjunctival circumlimbal injection of atropine, epinephrine, or both, frequently frees stubborn adhesions. DIONIN and the application of hot compresses several times daily promote absorption of exudate and bring relief. Local anesthetics will alleviate pain. Nonspecific therapy—sterile boiled milk intragluteally or typhoid vaccine intravenously—is useful.

If syphilis or other disease or a focus of infection is responsible, vigorous specific therapy should be instituted promptly.

Surgical treatment may be required for hypopyon, persistent posterior synechiae, secondary glaucoma, and the establishment of an artificial pupil.

Chorioretinitis. Therapy directed against possibly causative infectious diseases or foci of infection is essential. Foreign protein injections of milk, intramuscularly, or typhoid vaccine may hasten absorption of the exudates before permanent damage to the retina occurs. Atropine may be used to immobilize the uveal tract and help prevent spread of infection. Dark glasses and rest are indicated.

Optic neuritis. The underlying etiologic factor must be removed, if possible. Typhoid vaccine, intravenously, or other hyperthermic measures may be useful in cases due to multiple sclerosis or undetermined causes. Large doses of thiamine merit trial.

Sympathetic ophthalmia. Prompt, adequate treatment of an injured eye is of great importance in preventing sympathetic ophthalmia. The injured eye should be enucleated when sightless or when the preservation of sight is unlikely, especially when the ciliary body is involved. When there is useful vision in the injured eye, the question of enucleation is difficult, because signs of irritability often subside without developing into an active sympathetic inflammation. Enucleation of the injured eye is of no value once active inflammation has developed in the sympathizing eye.

Once sympathetic ophthalmia has developed, vigorous treatment may salvage some vision. Treatment has consisted of atropine, DIONIN, hot wet compresses, and foreign protein injections as in iridocyclitis. Sodium salicylate in large daily doses may be tried.

Skin Conditions

Favorable results have been obtained following the use of cortisone in many dermatologic conditions, both allergic and nonallergic. (*See* page 68.)

Allergic Skin Conditions

Angioneurotic edema, atopic dermatitis, and *exfoliative dermatitis,* including cases resulting from *drug allergy,* have shown striking response to cortisone therapy. Symptomatic relief is attained, external manifestations show regression or disappear and, in some instances, such as severe exfoliative dermatitis, a probably fatal outcome may be prevented.

Administration of cortisone has been successful in affording relief during the pruritic and inflammatory stages of allergic eczematous contact-type dermatitis. Severe cases of *rhus* (poison ivy) *dermatitis* in which other therapeutic agents have been ineffective, may yield to cortisone. Usually, only two to four days of treatment are required.

In *atopic dermatitis* results of cortisone therapy often are dramatic. Symptoms may improve within two or three hours; chronic lesions improve or disappear in about three days. Itching and eruptions in cases resistant to other forms of therapy may be alleviated. When eruptions that have been comparatively stationary again become active, retreatment with cortisone is indicated.

OTHER MEASURES

The cause of the allergy should be searched for and eliminated in order to prevent relapse. In all cases of allergy it is important not to overlook conventional management.

Patients with *atopic dermatitis* should be instructed to avoid emotional upsets as much as possible. Foci of infection, if present, should be appropriately treated. Soap substitutes should be used for routine cleansing, but too frequent baths and showers and undue exposure to the sun are not advisable. Known allergens should be avoided or appropriate desensitization procedures tried. Starch baths, or local applications of effective lotions, ointments, or compresses may be necessary to allay pruritus. Preparations containing phenol are contraindicated. Tar ointments or paints are helpful in the dry, lichenified stage, but not in the acute stage. Antihistaminic drugs often prove beneficial. If complicating pyogenic infection develops, it should be treated with appropriate antibiotics or chemotherapy.

Angioneurotic edema (*giant urticaria*) is a self-limited condition, generally lasting for one to two weeks, hence, treatment is chiefly palliative. Etiologic agents must be searched for and avoided or eliminated. Fluids should be forced and any medication not essential to the patient's life should be omitted until the acute allergic state has subsided. Antihistaminic drugs, calcium gluconate, or epinephrine may relieve itching and reduce swelling. Colloid baths and antipruritic lotions and powders also are helpful.

In *chronic urticaria*, autohemotherapy—removing 20 cc. of blood from a vein and immediately re-injecting into the buttocks—sometimes is beneficial. Thyroid extract has proved of benefit in a small number of cases. Any possible causative drug, especially headache remedies, sedatives, and soporifics, should be eliminated.

In cases of *drug reactions*, all drugs should be discontinued. Or, if this is not feasible, the drug most suspected should be stopped and replaced, if possible, by a chemically unrelated drug with similar physiologic action. Elimination of the causative drug from the body can be hastened by forcing fluids, and by administration of cathartics. In arsenical, bismuth, mercury, or gold-salt toxicity, BAL should be used. For iodine and bromide eruptions, sodium chloride 12 to 15 Gm daily is given to increase elimination of the offending ions. Antihistaminic drugs, or combinations of ephedrine and phenobarbital often are effective in urticarial eruptions.

Hospitalization is indicated for patients with extensive eczematous or exfoliative dermatitis and in those with extensive purpuric, hemorrhagic, or bullous manifestations.

In *poison ivy* and other forms of *contact dermatitis*, absolute cleanliness of the affected areas should be observed. Severe secondary infections may necessitate the use systemically of penicillin or the sulfonamides Itching and burning may be relieved by compresses of Burow's solution, starch baths, or lotions.

Nonallergic Skin Conditions

Cortisone frequently produces striking clinical results in many serious cases of nonallergic skin diseases that resisted former methods of treatment These diseases include pemphigus, scleroderma, and dermatomyositis.

Through use of the hormone, management of the patient with *pemphigus* often is greatly facilitated and more

economical, since in many cases the need for hospitalization or nursing service is eliminated. Remissions have been maintained throughout the treatment period, and, in some instances, after cessation of therapy.

Supportive measures employed in the treatment of grave systemic diseases are indicated. A high-caloric, high-protein diet plus vitamin supplementation is essential. Parenteral feeding and fluids must be given to patients unable to eat because of painful oropharyngeal lesions Repeated small blood transfusions, especially those from a pemphigus patient in remission, have been used by some clinicians. Crude liver extract also has been tried. Ultraviolet-ray therapy may produce beneficial results. Other conventional treatment utilizes various forms of arsenic—such as Fowler's solution and acetarsone—vitamin D_2, and injections of foreign protein, *e.g.*, boiled milk.

External measures include daily opening of bullae, and painting of the bases with a 1 per cent solution of gentian violet. Pressure dressings with petroleum jelly do much to promote healing and prevent formation of new bullae. The use of benzocaine in lotions is necessary at times to alleviate pain. Mouth lesions demand special attention. An aqueous solution of potassium permanganate can serve as a mouthwash and erosions should be treated with 5 per cent silver nitrate solution.

For bedridden patients, liberal sprinkling of the sheets with talcum containing 5 per cent benzocaine affords relief If the involvement of pemphigus is extensive, the patient may derive great benefit from immersion in a warm —not hot—bath consisting of 1:40,000 potassium permanganate solution for about twenty to thirty minutes several times daily.

In *scleroderma,* the results following treatment with cortisone frequently are far superior to those previously attained by any other method of therapy. Symptomatic im-

provement is particularly evident. The abnormal collagen pattern appears to be altered although the basic course of the disease is unchanged. Relapses, when they do occur, may respond to reinstituted cortisone therapy.

Other Measures. A balanced diet, preferably with general vitamin supplementation, should be maintained, although there is no evidence that scleroderma is due to nutritional deficiency. Methyl testosterone has caused regression of lesions and increased muscular strength in some cases. Thyroid extract, foreign protein injections, neostigmine, ammonium chloride, parathyroidectomy, and surgical correction of obvious endocrinopathies, each has proved beneficial in isolated instances. Measures to soften the skin and improve blood supply to the tissues may be useful; these include massage, warm baths, and bland ointments containing 1 per cent pilocarpine or 1 per cent salicylic acid. Niacin or acetylcholine by iontophoresis may promote vasodilatation.

Addison's Disease

Cortisone has become a major factor in the treatment of Addison's disease. (*See* page 82.) Beneficial effects following such replacement therapy include restoration of normal electro-encephalogram; normalization of red blood cell count, hemoglobin, and hematocrit values; improvement in electrolyte balance. Better morale, stamina, and appetite are achieved, and the occurrence of adrenal crises is repressed or eliminated.

Large doses of cortisone given orally to patients with Addison's disease in adrenal crisis, or complicated by infection, generally produce striking results within a few hours. If vomiting is a problem during crisis the value of cortisone is more limited, since the intramuscular preparation does not take effect as promptly as oral medication. Research on new formulations of cortisone for intravenous

use, currently under way, promises a solution to this problem in the near future.

It usually is practical to administer sodium chloride or desoxycorticosterone acetate in addition to cortisone. Other measures that are employed include: I.V. fluids to combat dehydration, glucose to counteract hypoglycemia, and chemotherapy to limit spread of infection.

In general, cortisone is contraindicated in known or suspected cases of tuberculosis. However, the dosage required for management of Addison's disease can be given safely in tuberculous patients if combined with chemotherapy, and an improvement in both conditions will often be produced. It should be kept in mind, of course, that tuberculosis is one of the more common etiologic factors that may result in hypoadrenalism.

Disseminated Lupus Erythematosus

Cortisone is the first agent observed to exert some measure of control over the progressive decline that usually occurs in patients with disseminated lupus erythematosus. (*See* page 85.) The hormone elicits the following beneficial effects in most cases where treatment is begun early enough in the course of the disease. (*1*) retardation of arthralgia, fever, skin lesions, and serositis, and an enhanced sense of well-being together with increased appetite and gain in weight; (*2*) stamina to go through stress and crises, such as major operations and infections, including pneumonia, abscesses, and septicemia, which ordinarily are fatal in this disease; (*3*) a degree of remission which, while it might occur in the natural course of the disease, is exceptional in acute phases.

Improvement usually persists from a few days to a few weeks or even longer. Symptoms may return within a short time after the hormone has been discontinued.

OTHER MEASURES

Gold salts, such as MYOCHRYSINE®, have been useful in the chronic stage but are contraindicated in the acute form of the disease. Patients should avoid direct sunlight. A well-balanced, high caloric diet is indicated. Transfusions will diminish the accompanying anemia temporarily and enhance the general sense of well-being. Rest is important in chronic cases since relapse often follows overexertion. Since acute lupus crisis often is caused by intercurrent infection, some clinicians have suggested that antibiotics be administered along with cortisone during the acute phase, and that antibiotics be continued in reduced dosage as adjuncts to the maintenance regimen of cortisone.

Other Indications

Endocrine disorders Cortisone frequently is lifesaving in the management of Waterhouse-Friderichsen syndrome and is essential in the pre- and postoperative care of patients who undergo bilateral or subtotal adrenalectomy. Because it decreases production of androgens by the adrenal cortex, cortisone may be of benefit also in cases of female pseudohermaphroditism or male adrenogenital syndrome attributable to adrenal hyperplasia.

In pituitary insufficiency, cortisone is highly effective. However, treatment with other appropriate hormones, e g., thyroid and gonadal, also may be required to restore the over-all clinical picture to normal.

The pre- and postoperative care of patients with pituitary tumors presents another indication for the use of cortisone. Spontaneous hypoglycemia in children also has responded well to cortisone This treatment should, of course, be reserved for those cases in which eliminable etiologic factors such as tumors of the pancreas cannot be demonstrated

use, currently under way, promises a solution to this problem in the near future.

It usually is practical to administer sodium chloride or desoxycorticosterone acetate in addition to cortisone. Other measures that are employed include: I.V. fluids to combat dehydration, glucose to counteract hypoglycemia, and chemotherapy to limit spread of infection.

In general, cortisone is contraindicated in known or suspected cases of tuberculosis. However, the dosage required for management of Addison's disease can be given safely in tuberculous patients if combined with chemotherapy, and an improvement in both conditions will often be produced. It should be kept in mind, of course, that tuberculosis is one of the more common etiologic factors that may result in hypoadrenalism.

Disseminated Lupus Erythematosus

Cortisone is the first agent observed to exert some measure of control over the progressive decline that usually occurs in patients with disseminated lupus erythematosus. (*See* page 85.) The hormone elicits the following beneficial effects in most cases where treatment is begun early enough in the course of the disease: (*1*) retardation of arthralgia, fever, skin lesions, and serositis, and an enhanced sense of well-being together with increased appetite and gain in weight, (*2*) stamina to go through stress and crises, such as major operations and infections, including pneumonia, abscesses, and septicemia, which ordinarily are fatal in this disease, (*3*) a degree of remission which, while it might occur in the natural course of the disease, is exceptional in acute phases.

Improvement usually persists from a few days to a few weeks or even longer. Symptoms may return within a short time after the hormone has been discontinued.

Confinement to bed is required for patients with fever, pulmonary hemorrhage, severe dyspnea, or concurrent respiratory infections, and for those in poor general condition. Symptomatic treatment is indicated for cough, fever, malaise, insomnia, or other troublesome manifestations.

Periarteritis Nodosa: When treated early with cortisone, encouraging responses have been noted in this disease; inflammatory reactions are quelled. When treated late in the course of the disease, response is poor and patients may die of complications despite healing of periarteritic lesions

Supportive and palliative measures, such as repeated transfusions, high caloric diet, and adequate sedation are indicated. Prompt repair of perforations of the gastrointestinal tract that often occur during this disease may circumvent fatal peritonitis.

Neoplasms: The value of cortisone as a palliative measure is being widely recognized in cases of *terminal cancer*, especially in carcinoma of the breast or prostate. In such patients, pain is frequently lessened, a feeling of well-being induced, and appetite and strength are improved.

Bursitis: Administration of cortisone has produced impressive results Within a few days after the initial dose of cortisone, normal range of motion may be restored and pain and tenderness abolished. Supportive measures should be employed along with cortisone therapy. Complete rest of the extremity in a sling or splint is desirable. Early active movements will aid in preventing the development of crippling adhesions. Pain is relieved by suitable analgesics, diathermy, or massage. Deep X-ray therapy sometimes proves useful. If effusion is pronounced, aspiration may be necessary.

Sarcoidosis· Prior to the introduction of cortisone, no specific treatment had been established for sarcoidosis Different methods including X-ray have been used without convincing results. Vitamin D_2 and dihydrotachysterol have produced some benefits.

A number of patients with pulmonary sarcoidosis have responded extremely well to cortisone with easily measurable physiologic changes. In some, radiologic changes reappear fairly soon after treatment is discontinued, but pulmonary incapacitation is greatly reduced. However, unless therapy is maintained, patients usually experience a relapse.

Berylliosis· Cortisone has produced good results, particularly in the pulmonary granulomatoses secondary to beryllium poisoning There was definite improvement in more than half the cases reported, and maintenance through the reduced-dosage technic proved feasible Dyspnea is promptly [illegible] Vital ca-

[illegible]

capillary Pulmonary hypertension may be reduced Following therapy, some patients can continue for several months without further administration of cortisone.

Treatment with CORTONE

(For treatment with HYDROCORTONE Acetate, *see* page 37.)

Clinical Response
Dosage
Case Histories

Three years of clinical experience with CORTONE have established this hormone as a dramatic and often lifesaving therapeutic agent. Hundreds of published reports have confirmed the beneficial results that CORTONE exerts in many diseases for which adequate treatment formerly did not exist.

Prolonged relief can be maintained in many cases While dosage of CORTONE is based chiefly on severity of the disease treated, it has become apparent that the large amounts employed in earlier studies are not always necessary. In chronic, nonfatal disorders (*e.g*, rheumatoid arthritis), use of smaller doses has made it possible to control cases satisfactorily over long periods and avoid undesired effects in many instances.

Careful adjustment and gradual reduction of dosage contributes to success of therapy Several dosage forms and concentrations of CORTONE are available to enable the physician to take full advantage of this effective agent. In addition to suspension for *intramuscular* injection, CORTONE can be given in tablets *orally*, or by *local* application of the ophthalmic preparations in diseases of the anterior segment of the eye.

Combined Therapy: In all cases under treatment, accepted methods of management must be utilized in order to secure optimal clinical response. Therapeutic agents and

Response to CORTONE *as Reported in Various Diseases*

BENEFICIAL EFFECT OFTEN DRAMATIC	RESULTS THUS FAR ENCOURAGING	TRANSIENT BENEFICIAL EFFECTS OBSERVED, BUT ULTIMATE PROGNOSIS UNALTERED
Rheumatoid Arthritis	[illegible]	[illegible] arly)
Rheumatoid Spondylitis	[illegible]	[illegible] or
Still's Disease	ENCOURAGING, BUT MAY BE VARIABLE	Lymphosarcoma
Psoriatic Arthritis		Chronic Lymphatic Leukemia
Acute Rheumatic Fever, especially with carditis	Acute Gouty Arthritis	Multiple Myeloma
[illegible]	[illegible]	[illegible] T
[illegible]	[illegible]	[illegible] ist
[illegible]	[illegible]	[illegible] er
[illegible]	[illegible]	[illegible] s
Edema	bocytopenic)	
Drug Sensitization	Allergic Purpura	
Serum Sickness	Agranulocytosis and certain forms of anemia (acquired hemolytic, occasional cases of aplastic)	
Exfoliative Dermatitis		
Atopic Dermatitis		
Pemphigus		
Inflammatory Eye Diseases	Retrolental Fibroplasia	
Adrenogenital Syndrome (due to [illegible]	Transfusion Reactions	
[illegible]	[illegible]	
	Sprue	
	Rh Incompatibilities	

Treatment with CORTONE

(For treatment with HYDROCORTONE Acetate, *see* page 37.)

Clinical Response
Dosage
Case Histories

Three years of clinical experience with CORTONE have established this hormone as a dramatic and often lifesaving therapeutic agent. *Hundreds of published reports have* confirmed the beneficial results that CORTONE exerts in many diseases for which adequate treatment formerly did not exist.

Prolonged relief can be maintained in many cases. While dosage of CORTONE is based chiefly on severity of the disease treated, *it has become apparent that the large* amounts employed in earlier studies are not always necessary. In chronic, nonfatal disorders (*e.g.*, rheumatoid arthritis), use of smaller doses has made it possible to control cases satisfactorily over long periods and avoid undesired effects in many instances.

Careful adjustment and gradual reduction of dosage contributes to success of therapy. Several dosage forms and concentrations of CORTONE are available to enable the physician to take full advantage of this effective agent. In addition to suspension for *intramuscular* injection, *CORTONE can be given in tablets orally, or by local* application of the ophthalmic preparations in diseases of the anterior segment of the eye.

Combined Therapy. In all cases under treatment, accepted methods of management must be utilized in order to secure optimal clinical response. Therapeutic agents and

general measures that are indicated as adjuncts CORTONE in various diseases, are summarized in Part I this *Handbook* (pages 1 to 19).

RHEUMATOID ARTHRITIS AND ITS VARIANTS

(*Rheumatoid Spondylitis, Still's Disease, and Psoriatic Arthritis*)

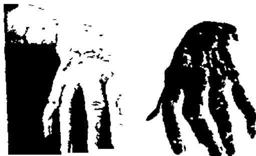
CORTONE has been used orally and parenterally in the treat ment of thousands of patients with rheumatoid arthriti In virtually every case reported in the extensive literat CORTONE has produced prompt remission of sympto and signs of the disease. Continued treatment is usuall though not always, necessary to maintain the therapeut effect.

Those cases of rheumatoid arthritis wherein CORTON has not proved effective, frequently have been the lat so-called burned-out cases, in which deformities are sever but active inflammation no longer is present.

The Clinical Response

The pattern of improvement has been remarkably consistent. Shortly after institution of treatment with CORTONE, the physician can expect a pronounced reduction of the patient's muscular stiffness, usually beginning within twenty-four to forty-eight hours after the initial dose Such relief may be noted as early as six hours after therapy is started, especially if relatively large dosage is employed and if the degree of inflammatory reaction present is not too great. Prompt response is particularly likely to occur when CORTONE is administered orally. In many patients, muscular and articular stiffness is significantly or completely

RHEUMATOID ARTHRITIS

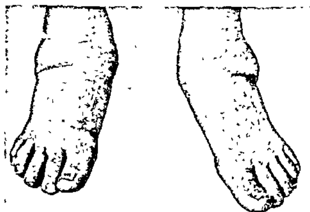


Prior to the administration of CORTONE

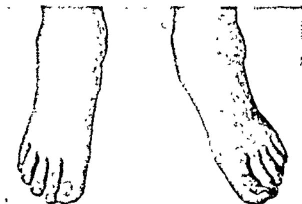


After treatment with CORTONE over a 16-day period

RHEUMATOID ARTHRITIS



Before treatment Periarticular swelling and hydrarthrosis



After treatment with CORTONE Diminution of pain, increased mobility, and visibly decreased effusion and swelling

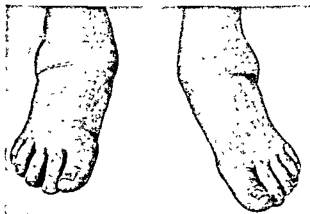
RHEUMATOID ARTHRITIS



Before treatment
Same disability as illustration, plate II



After treatment with CORTONE.
Same favorable response as illustration, plate II

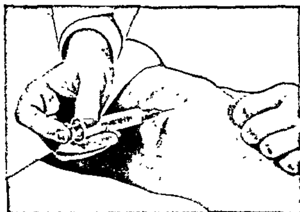


Before treatment Periarticular swelling and hydrarthrosis

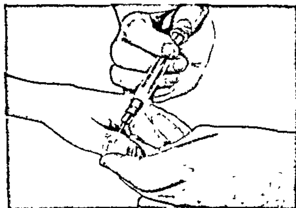


After treatment with CORTONE Diminution of pain, increased mobility, and visibly decreased effusion and swelling

Intra-articular Injection of HYDROCORTONE Acetate



Knee



Thumb



Rheumatoid nodules of occipital region of the scalp prior to therapy



The forty-fourth day of therapy with CORTONE, 100–200 mg daily

RHEUMATIC FEVER

Female, 15 years, Acute Rheumatic Fever with Polyarthritis and Carditis, Four Days' Duration: First Attack

Temperature 101 99 97

Pulse Rate 120 80 40

P-R Interval Seconds .24 .24 .24 .20 .18 .16 .14 .16 .14 .16

Sedimentation Rate mm /hr 120 90 60 30

CORTONE* mg /day 200 100 0

4 8 12 16 20 24 28

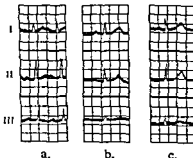
Days

*(While the above dosage proved effective in this instance, the *present recommended regimen employs a more adequate dosage*)

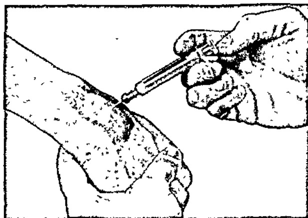
a Admission ECG P-R *int* = *24 sec*

b *After 4 days'* ℞ with CORTONE, P-R *int* = *20*

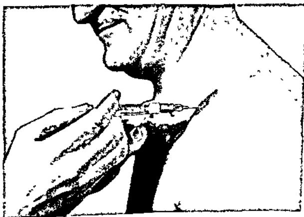
c *After 8 days'* ℞ P-R *int* = *16*



Intra-articular Injection of HYDROCORTONE Acetate



Wrist

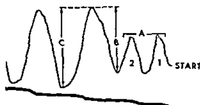


Shoulder

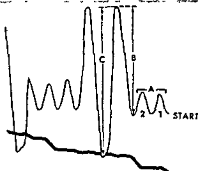
BRONCHIAL ASTHMA

Increased Vital Capacity—an objective measure of the effectiveness of CORTONE

A. Tidal breathing
B. Complemental air
C. Vital capacity



Typical spirogram of asthmatic Note marked diminution in vital capacity and complemental air, also, the over-all lengthening of the interval between inspiration and expiration



This spirogram illustrates the improvement that may be expected in asthmatics following the administration of CORTONE Note in particular the increase in vital capacity.

RHEUMATIC FEVER



Before therapy
with CORTONE



After conclusion of
three weeks' treatment
with CORTONE

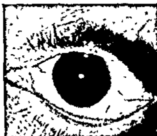


One month later

SECONDARY IRITIS



Before treatment



After topical use of CORTONE

ALLERGIC CONJUNCTIVITIS

Before treatment



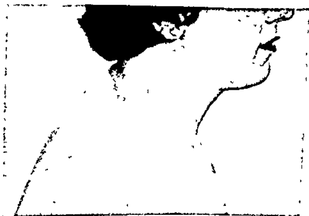
After topical use of CORTONE



BRONCHIAL ASTHMA



Before treatment



After treatment with CORTONE Note relaxation of accessory muscles of respiration

POSTOPERATIVE UVEITIS



Before treatment

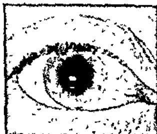


After topical use of CORTONE

KERATOCONJUNCTIVITIS



Before treatment



After topical use of CORTONE

CONJUNCTIVITIS DUE TO EXPOSURE TO CHEMICAL IRRITANT

Topical CORTONE as suspension and ointment applied over five-day period to one eye only. Photographs show the more rapid clearing of the eye treated with CORTONE





Before treatment

After 48 hours



Untreated eye



Eye treated with CORTONE

ATOPIC DERMATITIS



Before treatment

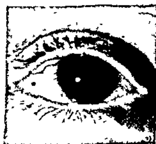


After six days of treatment with CORTONE

CORNEAL ULCER
and Hypopyon



Before treatment

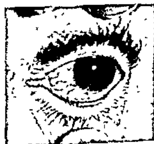


After therapy with CORTONE

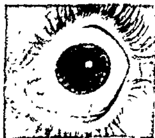
IRIDOCYCLITIS

CORTONE administered parenterally and as ointment topically

Before treatment



After 7 days of treatment



ATOPIC DERMATITIS

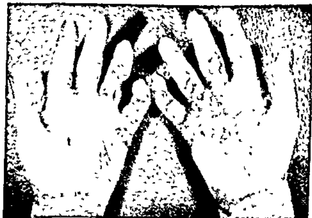


Before treatment

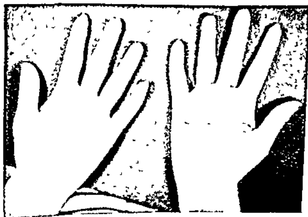


After eight days
of treatment
with CORTONE

ATOPIC DERMATITIS

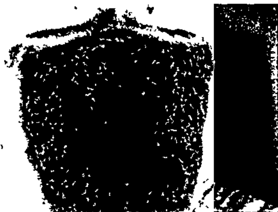


Before treatment

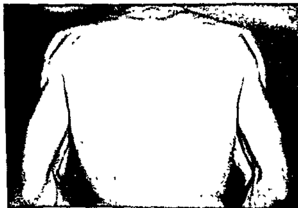


After four days of treatment with
oral CORTONE, 100 mg daily

EXFOLIATIVE DERMATITIS



Before treatment—erythema over entire body with exudation, crusting, and exfoliation

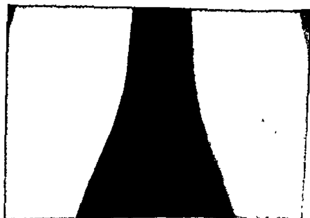


After four days of parenteral therapy with CORTONE

ATOPIC DERMATITIS



Before treatment



After nine days of oral use of CORTONE



Exfoliative dermatitis before treatment



After treatment with CORTONE

EXFOLIATIVE DERMATITIS



Before treatment



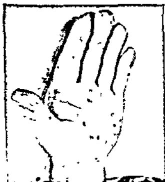
After 8 weeks of treatment with CORTONE

CONTACT DERMATITIS



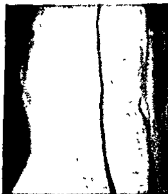
Before treatment

Severe dermatitis of hand resulted from contact with detergent solution



Following therapy with CORTONE

DRUG ALLERGY

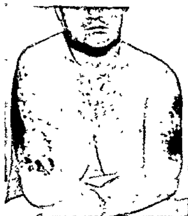


Penicillin sensitivity
before therapy

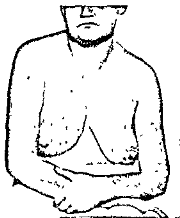


Disappearance of eruptions
following therapy
with CORTONE

DISSEMINATED LUPUS ERYTHEMATOSUS



Before treatment



After treatment with CORTONE

SCLERODERMA



Collagen pattern before treatment with CORTONE; x 200



Collagen pattern six weeks after treatment with CORTONE, x 200

SARCOIDOSIS



Before treatment



After one month of treatment with CORTONE



Before treatment



After 22 days of treatment with CORTONE

BURSITIS

Increase in Range of Motion

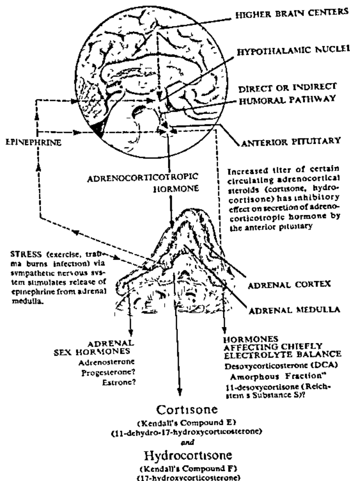


Before treatment with CORTONE

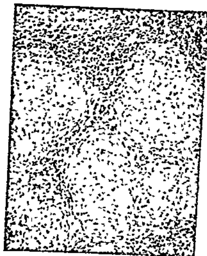


Ninety-six hours after starting treatment with CORTONE

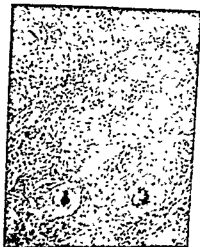
PITUITARY-ADRENAL RELATIONSHIPS



SARCOIDOSIS



Femoral lymph node
(low power)
before treatment



After 39 days of
treatment with CORTONE

relieved within a few days. Following this, there is a decrease in or complete disappearance of aching and pain on motion, articular tenderness, and, finally, articular swelling. In many patients, mild soft-tissue deformities about the joints, and subcutaneous nodules, disappear within seven to ten days. Muscular strength and articular function may return to a remarkable degree within a few days, despite muscle atrophy and previously restricted joint motion

In early and less severe cases of the disease treated with CORTONE, complete remission often occurs, with disappearance of all symptoms and abnormal physical signs; in cases of longer standing, some joint swelling and effusion may persist even though all symptoms are relieved. Flexion deformities, soft-tissue changes, bursitis, tenosynovitis, enlarged lymph nodes, and subcutaneous nodules usually improve or disappear; existing destructive changes of cartilage and bone, ankylosis, and ligamentous calcification necessarily remain unaltered Judicious application of physical therapy[7, 14] should be employed in conjunction with administration of CORTONE (*see* page 2).

Concomitant with the improvement of arthritic manifestations, there is a comparable gain in appetite, weight, and strength, frequently with a marked feeling of well-being and improvement in mental attitude, occasionally within several hours after initial administration of the hormone Patients who have been depressed and ill-natured, with hopeless or resigned outlooks, usually become cheerful, hopeful, and even elated within a few days after treatment with CORTONE is begun Increased mental activity and capacity frequently are evident, and are often expressed through purposeful and gainful activity.

After treatment with CORTONE is discontinued, relapse generally occurs, sometimes promptly, but occasionally slowly Some patients retain the greater part of the remission of arthritic manifestations for weeks or months

WE ARE GRATEFUL TO THE FOLLOWING FOR THE CLINICAL PHOTOGRAPHS APPEARING ON THE PRECEDING PLATES—I-XXX

Alvan L. Barach, M D, New York. IX, X

E P. Engleman, M D, M A Krupp, M D, and M G Molyneaux, M.D, San Francisco, Calif IV, XXI.

Eugene M Farber, M D, San Francisco, Calif. XVII, XXIV

S. M Hoch, M D, Rahway, N.J.: XII, XXVIII

Joseph Lee Hollander, M D, Philadelphia, Pa: V, VI.

Freddy Homburger, M D, Boston, Mass XVI.

John F Johnson, M D, Plainfield, N J XX.

Hedwig S Kuhn, M D, Hammond, Ind XI, XIII *(bottom)*, XIV *(top)*

Henry J Lehnhoff Jr, M D, Omaha, Neb XIX, XXII

Irving H Leopold, M D, Philadelphia, Pa XIII *(top)*

Charles Ragan, M D, New York II, III

Louis E Siltzbach, M D, New York XXIX XXX

Tom Spies, M D, Birmingham, Ala XXIII

Marion B Sulzberger, M D, and Victor H Witten, M D, New York XV, XVIII, XXV

Matthew Taubenhaus, M D, and Maurice Lev, M D, Chicago, Ill XXVI [*A M.A Arch Int Med* 87 583-593, April 1951]

Herman H. Tillis, M D, Newark, N J I

doses of 25 mg. four times daily, with meals and at bedtime) for seventeen days. Improvement began approximately fourteen hours following the first dose when the patient noticed less aching and stiffness and greater mobility in fingers and wrists. Subjective improvement was considerable within twenty-four hours and she was able to walk with more assurance and less pain. After forty-eight hours, swelling of the metacarpophalangeal and proximal interphalangeal joints began to recede, appetite improved, and fatigue lessened. On the sixth day of treatment, she walked almost normally, and could feed herself, dress, and comb her hair with ease and little discomfort.

Objective manifestations subsided steadily. By the seventeenth day of therapy with CORTONE, over-all improvement was graded as about 80 per cent. There still was some tenderness [illegible] creased to 39 mm. per hour. The patient had gained seven pounds. Her face was slightly rounded and there was mild edema of the lower legs, despite strict adherence to a low salt diet.

[illegible]

after discontinuance of therapy. If CORTONE is re-administered when manifestations of the disease return, prompt remission is again induced in most cases. The use of continuous, low dosage therapy with CORTONE (*see* page 34) precludes relapse and maintains adequate relief in many cases.

The following reports show the response to CORTONE in mild as well as in more severe cases of rheumatoid arthritis.

Case A: [8]

RHEUMATOID ARTHRITIS—*Adjustment of Maintenance Dosage*

This case illustrates (1) initial suppressive therapy and gradual dose reduction, (2) determination of individualized maintenance doses for adequate symptomatic control, (3) good control with rehabilitation over an extended period, achieved safely through moderate dosage, (4) necessity of adjusting maintenance dosage to offset exacerbations of disease activity; (5) adjustment of dosage—within a small range—prescribed for the intelligent patient who uses symptoms as a guide; (6) supportive treatment with salicylates during periods of emotional or physical strain

Prior to Therapy with CORTONE—Woman, age 39, had moderately severe arthritis of sixteen months' duration, and lost 23 pounds over this period. The disease began insidiously but progressed steadily. Multiple joints became involved, including

in dressing, combing her hair, and feeding herself, and walked

Response to CORTONE—On August 21, 1950, 150 mg. of CORTONE were given orally, followed by 100 mg daily (in divided

progressed rapidly thereafter, involving the knees, wrists, proximal interphalangeal, metacarpophalangeal, metatarsophalangeal, and temporomandibular articulations bilaterally.

In 1948, the patient improved moderately following chrysotherapy, rest, physiotherapy, and general supportive measures. The improvement continued for two years, but was not great enough to permit her to work. In 1950, gold salt therapy was interrupted because of skin rash and leukopenia. Greater disability ensued. Manifestations in the knees became particularly pronounced, with marked flexion deformity and development of

the Westergren method

less. The erythrocyte sedimentation rate was reduced to 28 mm per hour.

Gradual Reduction of Dosage—The daily amounts of CORTONE were reduced gradually by 12.5 mg every seven days. The patient continued to improve. She walked almost normally. After thirty-nine days of treatment, the sedimentation rate was

made three times, but this amount was found insufficient On April 15, 1951, she went back to work as a cashier, and since then has worked full time. No undesirable effects have been observed except for very slight hypertrichosis of the face which

observer. Some restriction of caloric intake was necessary to prevent excess weight gain. Highly salted foods were avoided. The patient was able to carry on normal social and household activities with little discomfort. She obtained nine hours of bed rest at night and one to one and a half hours at mid-day. She did not indulge in strenuous physical activity.

In July 1951, the patient's son developed a serious illness and for about six weeks she was under great emotional and physical strain. Rheumatic manifestations were intensified and maintenance dose of CORTONE had to be raised to 75 mg. a day, in addition to 20 to 30 grains of salicylates, in order to uphold marked improvement. When the son recovered, the arthritis became less active and maintenance dose was lowered again to 50 mg. a day. Control of the disease remained fairly stable for the next three and a half months, with increase of dosage to 62.5 mg. a day for several days on four occasions to offset temporary increases in disease activity.

In December 1951, the patient was provided with 5-mg *tablets* of CORTONE and was instructed to alter her own maintenance dose, depending on the severity of symptoms. She was advised to divide the total daily dose into four fairly equal amounts and to keep dosage within a range of from 30 to 70 [illegible]

[illegible]

Case B: [3]

RHEUMATOID ARTHRITIS—Prolonged Maintenance Dosage

This case illustrates that many patients may be rehabilitated with moderate, uninterrupted doses of CORTONE *over long periods. It shows, too, how certain patients may be maintained adequately with relatively constant low dosage.*

Prior to Therapy with CORTONE—A 26-year-old woman had chronic rheumatoid arthritis for six years. The disease began insidiously in 1944 with mild but persistent aching and stiffness in various peripheral joints, especially the wrists and proximal interphalangeal joints bilaterally. In August 1945, following an acute pharyngeal infection, actual articular swelling and limitation of motion developed. The rheumatoid arthritis

right knee The sedimentation rate dropped from 117 mm. per hour to 51 mm per hour. The patient gained weight gradually and was generally improved.

Case D·[12]

RHEUMATOID ARTHRITIS—*Eight Years' Duration*

This case report shows clearly that the physician, by reduction of daily dosage, can find "the minimum dose that causes no side effects, yet reduces symptoms to a minimum" Relief of 90 per cent of symptoms was obtained in this patient on a maintenance dose of 50 mg. a day Patient was able to return to work as a metal-parts packer within three weeks after starting treatment with CORTONE.

Prior to Therapy with CORTONE—For eight years, a 52-year-old man complained of intermittent pain, stiffness, and swelling of the elbows and ankles. The illness began with increased fatigability, loss of energy, pain, tenderness, stiffness, and swelling of multiple joints He had had many remissions and exacerbations, the latter often preceded by respiratory infections and emotional disturbances Several weeks prior to admission, there was a striking increase in symptoms and signs of acute arthritis.

The examination showed acute pain and limitation of motion in the large joints and swelling of the proximal interphalangeal joints of the fingers.

Response to CORTONE—CORTONE was given as follows:

250 mg.—first day
200 mg—second day
100 mg—third to fourteenth day
75 mg—fifteenth to twenty-second day
50 mg—daily for ten months

Within the first twenty-four hours, the patient noted symptomatic improvement with loss of pain and decreased stiffness Within three days the swelling of the joints had diminished He was able to move all of his joints without pain or discomfort;

has not been of concern to the patient. Her weight has reached 118 pounds, a total gain of 34 pounds. The sedimentation rate has remained within normal limits, and no new joint involvement has occurred. Throughout treatment, she avoided extra salt in food; recently, caloric intake was curtailed to prevent further weight gain. At this time, she is able to provide the entire financial support for herself and her semi-invalid mother.

Case C. [14]

RHEUMATOID ARTHRITIS—CORTONE *Combined With Physical Therapy*

Patients with rheumatoid arthritis who have limited articular function and who are being treated with CORTONE *may benefit further by a carefully individualized and supervised program of physical medicine. Martin, et al., reported on a series of patients, one group of which had had arthritis for five years or more. In this group, results were better with physical therapy plus* CORTONE *than with physical therapy alone. As illustrated in the following report, the best results were obtained in patients with relatively milder forms of the disease requiring treatment for relatively short periods.*

Prior to Therapy with CORTONE—An 18-year-old girl had active rheumatoid arthritis for one and a half years. The shoulders, elbows, wrists, and knees were involved. There was a flexion contracture of the right knee with marked synovitis, roentgenographic examination revealed narrowing of the joint space. This joint was so painful that the patient had not walked for one month prior to admission.

[illegible]

taught to walk in parallel bars. [illegible] gradually to walking with two canes, then one cane. Finally, she was able to walk without a cane, with no limp—and without pain in the

Case F: [13]

RHEUMATOID ARTHRITIS—*In Old Age*

In the aged, too, effective relief of symptoms may be maintained with conservative dosage of CORTONE.

Prior to Therapy with CORTONE—Man, age 80, had migratory polyarthritis for slightly more than a year. Past treatment included penicillin, desoxycorticosterone with ascorbic acid, and gold, minor improvement followed chrysotherapy. The patient could walk to the bathroom with great difficulty, but otherwise was confined to his room Blood pressure was 140/80. Motion was restricted in shoulders, elbows, wrists, fingers, knees, and ankles There was effusion about both wrists, knees, and ankles Rheumatoid nodules were present on both ulnar aspects of the forearms. Atrophy of the skeletal musculature was extensive. The sedimentation rate was 23 mm per hour, Cutler method.

Response to CORTONE—On November 9, 1950, 100 mg. of CORTONE per day were administered intramuscularly. Within four days the patient was almost free from pain and could walk [illegible] sure was 190/96, and he had gained two pounds When salt was restricted and 50 mg of CORTONE were given daily, orally, the blood pressure became 146/74 and has been maintained at about that level Following indiscreet use of salt in March 1951, moderate fluid retention and potassium deficit developed but were corrected by stringent limitation of sodium and by giving potassium orally [illegible]

[illegible] weeks. The resultant return of symptoms was followed by prompt relief upon resumption of CORTONE On the lower dosage of CORTONE the sedimentation rate rose to 29 mm. per hour. There was no hyperglycemia or glycosuria

He requires only 50 mg. of CORTONE a day for at least 90 per cent relief of all symptoms.

Case E. [16]

RHEUMATOID ARTHRITIS—*Forty Years' Duration*

Treatment with CORTONE *enabled this patient with arthritis, of many years' duration, to return to work as a switchboard operator. For more than six months, maintenance dosage has been only 37.5 mg. daily, given orally.*

Prior to Therapy with CORTONE—Female, age 61, with a forty-year history of rheumatoid arthritis, was first seen in November 1950 The disease was of rather low grade activity with short periods of flares and relative quiescence. However, ten months before examination, the patient developed increasing stiffness, swelling, and pain in hands, shoulders, knees, and feet. She was forced to give up a part-time job and had to have help for her housework

Response to CORTONE—CORTONE was given intramuscularly, *150 mg. daily for tw*
tions then were giver
objective improveme
total of 2 5 Gm of
tion rate rose to the pretreatment level.

given orally. Striking improvement occurred, but was lost on

daily, in divided doses, since then 37 5 mg per day. For several months, the patient has worked full time at a telephone switchboard, in addition to doing her housework. Every two weeks

alysis.
cept for slight ankle edema when dosage was 100 mg. daily.

On July 21, 1951, the patient's condition still was excellent and dosage was reduced to four tablets twice a week. At reexamination, January 13, 1952, her back was free from pain and function was almost completely restored. Blood count was normal Sedimentation rate (48 mm. per hour before treatment) now was only 15 mm by the Westergren method The patient is being maintained on a dosage of four 25-mg. tablets of CORTONE every three or four days

Administration and Dosage in Rheumatoid Arthritis

GENERAL CONSIDERATIONS—Dosage of CORTONE in each case should be adjusted to individual requirements, taking into consideration the natural history of the disease being treated. The required dosage varies considerably and depends more on the severity of the disease process than on age, surface area, or body weight of the patient. The objective in all cases is to obtain the maximum therapeutic response with minimum dosage of CORTONE.

The therapeutic effects are similar and the dosage is approximately the same, whether CORTONE is administered parenterally or orally. A change from one route of administration to the other may be made at any time during treatment without disturbing the clinical response. The action of CORTONE administered orally is more rapid and less prolonged than when given parenterally. Parenteral *injections may be given at twenty-four to forty-eight-hour* intervals for maintenance dosage; oral doses are administered every six to twelve hours to ensure sustained effect.

When changing from parenteral to oral administration, it is important to remember that CORTONE continues to act for twenty-four to forty-eight hours following injection.

Case G:[6]

RHEUMATOID SPONDYLITIS

Response to CORTONE *in rheumatoid spondylitis may be highly satisfactory, as shown in this case. At the first examination, the patient was tearful and in great pain Now, almost a year and a half after institution of therapy with* CORTONE, *she leads a perfectly normal life with quite strenuous social activities; the patient is practically free from pain on four 25-mg tablets of* CORTONE *every three or four days, and never has shown any untoward effects from this dosage*

Prior to Therapy with CORTONE—Patient, age 44, was examined October 3, 1950. She had had diffuse pain and stiffness in her back since 1943, unrelieved by X-ray treatment Physical findings were not significant except for the back. Patient stood with flattened lumbar curve and body tilted slightly to the left Flexion of the spine was markedly limited, particularly in the dorsal and lumbar regions, where flexion was almost absent Lateral movement and hyperextension of the spine were limited and painful. A spot over the fifth dorsal spinous process was exquisitely tender. X-rays of thoracic and lumbar spine revealed almost complete obliteration of sacro-iliac joints and bamboo-stick appearance of vertebrae from the twelfth thoracic to the third lumbar, inclusive, with lateral osseous bridging of the involved vertebrae The intervertebral joints were indistinct, and completely obliterated in the lumbar region The condition was diagnosed as rheumatoid spondylitis

Response to CORTONE—On October 9, 1950, 200 mg of CORTONE were administered intramuscularly, and 100 mg per day [illegible] weeks [illegible] om [illegible] NE [illegible] he [illegible] as [illegible] ifo [illegible] juice were given because patient complained of cramp-like pains in the legs Itching skin prompted reduction of dosage to 100 mg twice weekly. Itching was relieved; moonface appeared.

CORTONE now was given orally, starting with four 25-mg. tablets a day every other day The patient's condition was excel-

lent. On January 23, a mild exacerbation followed overexertion

and dosage was reduced to four tablets twice a week. At reexamination, January 13, 1952, her back was free from pain and function was almost completely restored. Blood count was normal Sedimentation rate (48 mm per hour before treatment) now was only 15 mm by the Westergren method. The patient is being maintained on a dosage of four 25-mg. tablets of CORTONE every three or four days.

Administration and Dosage in Rheumatoid Arthritis

GENERAL CONSIDERATIONS—Dosage of CORTONE in each case should be adjusted to individual requirements, taking into consideration the natural history of the disease being treated. The required dosage varies considerably and depends more on the severity of the disease process than on age, surface area, or body weight of the patient The objective in all cases is to obtain the maximum therapeutic response with minimum dosage of CORTONE.

The therapeutic effects are similar and the dosage is approximately the same, whether CORTONE is administered parenterally or orally. A change from one route of administration to the other may be made at any time during treatment without disturbing the clinical response. The action of CORTONE administered orally is more rapid and less prolonged than when given parenterally Parenteral injections may be given at twenty-four to forty-eight-hour intervals for maintenance dosage; oral doses are administered every six to twelve hours to ensure sustained effect.

When changing from parenteral to oral administration, it is important to remember that CORTONE continues to act for twenty-four to forty-eight hours following injection.

Therefore, it is advisable to begin with low oral doses, increasing to the full maintenance dosage only after twenty-four to forty-eight hours; thus, possible overdosage may be avoided. Conversely, when changing from oral to parenteral administration, oral therapy should be continued in reduced dosage for twenty-four hours after the initial parenteral injection, so as to tide the patient over the time lag in absorption from the intramuscular site. Injections should be made intramuscularly only, *never intravenously*.

Ever-growing clinical experience with CORTONE reveals that satisfactory results often can be obtained for prolonged periods with dosages substantially lower than those used in earlier studies. In practical management of rheumatoid arthritis, complete inhibition of symptoms frequently is unnecessary. Conservative dosage will produce satisfactory control in many patients and permit them to resume most of their usual activities. At the same time, lower dosage minimizes the incidence of objectionable hormonal effects.

Conservative dosage recommendations are based on successful experience with:

1. More conservative *initial* dosage.
2. Gradual *reduction* of dosage as soon as moderate relief is obtained.
3. Individualized *maintenance* dosage—smallest dose consistent with satisfactory, not necessarily complete, control of symptoms.

CONSERVATIVE DOSAGE — (when long-continued treatment may be required):

a. ORAL: *Initial Dosage:* 100 mg. per day. One 25-mg. tablet

than 10 to 12 5 mg. to the smallest suitable maintenance level. Either the scored 25-mg. tablets or the 5-mg. tablets may be conveniently utilized.

b. PARENTERAL (intramuscular): *Initial Dosage*· 100 mg. every twenty-four hours until the desired degree of remission is obtained. (Usually one to two weeks.)
Maintenance Dosage: After the desired effect is obtained, dosage should be reduced gradually by steps of not more than 10 to 12 5 mg to the smallest suitable maintenance level.

ACCELERATED DOSAGE—(when maximum and rapid response is desired):

a. [illegible]

[illegible]

b. PARENTERAL (intramuscular): *Initial Dosage*· 100 mg every eight hours for three doses; *then,* 100 mg. every twelve hours for two doses, *then,* 100 mg every twenty-four hours until the desired effect is obtained.
Maintenance Dosage After the desired effect is obtained, dosage should be reduced gradually by steps of not more than 10 to 12 5 mg to the smallest suitable maintenance level.

Withdrawal of treatment When it is desired to interrupt or discontinue treatment, the hormone should not be withdrawn suddenly but by gradual step-wise reduction of dosage.

VARIATIONS IN DOSAGE: Rheumatoid arthritis and certain other amenable diseases are subject to natural fluctuations in severity, remissions, and exacerbations. Furthermore, the disease may be affected by intercurrent episodes of unusual stress, such as accompany emotional

upsets and physical exhaustion. It is essential to provide for these varying conditions by temporary increases or decreases in dosage. It may be desirable to interrupt therapy occasionally, long enough to determine whether there has been a remission.

REST PERIODS: A rest period, if considered desirable, should be developed by step-wise reduction of dosage and last at least two weeks to permit resumption of adrenal activity. However, with the smaller maintenance doses now preferred, treatment may be continued for many months when the customary recommended observations are made

PREVENTION OF DEFORMITIES: It must be emphasized here that all the accepted measures of good supportive treatment, adequate diet, physiotherapy, orthopedic measures, nursing care, and sufficient rest must be utilized in order to prevent, correct, or minimize anatomic deformities associated with rheumatoid arthritis, and to support the general health and morale of the patient. CORTONE is very effective in the treatment of active, inflammatory disease, but its use must not preclude the necessity of planning and carrying out all measures that have proved useful in the past in the rehabilitation of patients. (*See* page 2)

SELECTED REFERENCES

1 Bilka, P. J.: *Minnesota Med* 34: 1088–1091, November 1951.

2 Boland, E. W : *Brit. M. J.* 2: 191–199, July 28, 1951.

[illegible]

6 Copeman, W. S C., *et al* [illegible] 23, 1952.

7 Coss, J. A., Jr., and Ragan, C. A.: *Arch. Physical Med* 32: 572–574, September 1951.

[8] Fischer, F., and Gillmor, C. S.: *J. Missouri M. A.* 49: 123–129, February 1952.
[9] Freyberg, R. H., *et al.*: *J.A.M.A.* 147: 1538–1543, Dec. 15, 1951.
[10] Hench, P. S.: *Ann. Int. Med.* 36: 1–38, January 1952.
[11] Kaufman, W.: *Ann. Allergy* 10: 47–52, January–February 1952.
[12] Keefer, C. S.: Personal Communication.
[13] Kuzell, W. C., and Schaffarzick, R. W.: Personal Communication.
[14] Martin, G. M., Polley, H. F., and Anderson, T. P.: *J.A.M.A.* 148: 525–528, Feb. 16, 1952.
[15] Personal Communication.
[16] Rose, D. L., and Kendell, H. W.: *J.A.M.A.* 148: 1408–1413, April 19, 1952.
[17] Rosenberg, E. F.: *Indust. Med. & Surg.* 21: 67–70, February 1952.
[18] Snow, W. B., and Coss, J. A.: *New York State J. Med.* 52: 319–322, Feb. 1, 1952.
[19] Sperling, I. L.: *J. M. Soc. New Jersey* 49: 29–32, January 1952.
[20] Ward, L. E., *et al.*: *Proc. Staff Meetings, Mayo Clin.* 26: 361–370, Sept. 26, 1951.

HYDROCORTONE ACETATE

Treatment of Rheumatoid Arthritis and Osteoarthritis by Intra-Articular Injection

Hydrocortisone (now identified by the registered trademark HYDROCORTONE), also known as Kendall's "Compound F" or Reichstein's "Substance M," is a distinct hormone and differs from cortisone. Both, however, belong to the series of hormonal substances isolated from extracts of the adrenal cortex, and both were synthesized from a bile acid in the Research Laboratories of Merck & Co., Inc. It has been suggested that hydrocortisone is the corticoid with

the most marked anti-inflammatory action at the tissue level.

HYDROCORTONE Acetate, injected into the articular cavity of a rheumatoid or osteoarthritic joint, produces *local* relief and is without generalized systemic effects when administered as recommended.

Injection of HYDROCORTONE Acetate is particularly useful.

1. When only one or two peripheral joints are affected by rheumatoid arthritis.
2. When only a few peripheral joints are actively inflamed, even though others have been ankylosed.
3. To relieve symptoms in those joints affected most severely, in cases where cortisone or corticotropin is contraindicated.
4. When the maintenance dosage of cortisone produces amelioration of symptoms in all but a few of the *most severely involved joints.*
5. When an acute exacerbation of inflammation occurs in one or a few joints.
6. When orthopedic correction of joint deformity has been or is to be undertaken.
7. In osteoarthritis, when there is an involvement of one or a few joints (knee or hip).

HYDROCORTONE Acetate *should not be used in any specific infectious arthritis (such as gonococcal or tuberculous).*

The Clinical Response

Significant improvement is usually achieved within a period of twenty-four hours after the intra-articular injection of HYDROCORTONE Acetate; swelling and tenderness decrease and range of motion increases markedly. After each injection, intra-articular joint temperature—which reflects changes in joint inflammation—is decreased significantly

(0.4° to 3.0°) and returns to pretreatment level in about four days. The clinical improvement that follows the injection of 25 mg of HYDROCORTONE Acetate may be expected to persist for three to twenty-one days. The subjective improvement in pain and stiffness of the joint may last even longer.

When used as directed, HYDROCORTONE Acetate causes a marked reduction in the total cell count of the synovial fluid. High cell counts are associated with rheumatoid arthritis, low counts with traumatic effusions and exudates.

The normal cell count of synovial fluid may be considered to be below 180; the average differential count is 63 per cent mononuclear phagocytes, 25 per cent lymphocytes, 7 per cent polymorphonuclear leukocytes, 3 per cent synovial cells, and 2 per cent unidentified cells. The total leukocyte count and the percentage of polymorphonuclear leukocytes are increased in rheumatoid arthritis. Normally, erythrocytes are not present.

This method of treating an inflamed joint, as described on page 41, will ameliorate but not cure the joint symptoms; it does not affect the cause of the joint inflammation. Conventional management should accompany therapy with HYDROCORTONE Acetate.

DEGREE OF IMPROVEMENT

The degree of local improvement that can be obtained through intra-articular injection of HYDROCORTONE as reported by Hollander, *et al.*,[1] is illustrated in the following table:

Diagnosis and Joint Injected	Number of Cases	Dosage of HYDROCORTONE Acetate (mg)	Degree of Local Improvement
Rheumatoid Arthritis			
One or both knees	62	25 mg in 51 37.5 in 11	4+ in 13, 3+ in 35 2+ in 12, 1+ in 2
Ankle	4	25	4+ in 1, 3+ in 1 2+ in 2
Elbow	4	15–20	3+ in 2, 2+ in 2
Shoulder	3	25	3+ in 2, 2+ in 1
Hip	3	25	4+ in 1, 2+ in 2
Wrist	3	15	2+ in 2, 0+ in 1
Metacarpo-phalangeal	1	10	3+
Osteoarthritis			
One or both knees	37	25	4+ in 22, 3+ in 14 2+ in 1
Hip	2	25	3+ in both
Terminal pha-langeal (Heberden's Node)	2	5	3+ in 1, 2+ in 1
First metatar-sophalan-geal	1	10	4+

4+ benefit: Local complete remission—complete absence of pain, swelling, tenderness, or limitation of function

3+ [illegible]

2+ [illegible]

1+ [illegible]

0 [illegible] none.

DURATION OF IMPROVEMENT

Rheumatoid Arthritis—In all 69 patients in a series reported by Hollander, *et al*,[1] injection of HYDROCORTONE Acetate into one or more joints "has resulted in prompt local alleviation of symptoms and signs . . . the duration of benefit from each injection has varied from a few days to several weeks Repeated injections have been equally effective."

Osteoarthritis—Thirty-nine patients with osteoarthritis were studied by Hollander, *et al.*[1] In all these patients, injection of HYDROCORTONE Acetate into one or more joints "has resulted in prompt relief of symptoms and signs." Duration of relief was "usually three weeks or longer, and often persisted until the patient abused the affected joint in some way. . . Repeated injections are equally effective and may maintain remission of symptoms for long periods."

Administration

(*See also* ILLUSTRATIONS, *Plates* V–VI)

Intra-articular injection of HYDROCORTONE Acetate may be performed as an office or clinic procedure requiring no elaborate preparation. The approach to the articular space will vary with the joint. The injection of HYDROCORTONE Acetate into the knee-joint cavity is a relatively simple procedure, particularly if effusion is present. Introduction into other joints varies in difficulty. It therefore is suggested that before making the injection, particularly into joints other than the knee, the physician should review the anatomic relationships involved and acquaint himself with the procedure.

Care must be taken in inserting the aspiration needle (20 gauge or larger) because it is intended that the hormone be placed within the joint cavity. Accidental injection of HYDROCORTONE Acetate in the surrounding tissues is not harmful but may decrease the effectiveness. Routine

sterile precautions are necessary. The use of a local anesthetic is elective. The site of injection should be selected carefully and the needle inserted quickly through the skin, subcutaneous tissue, joint capsule, and synovial membrane The withdrawal of a few drops of synovial fluid is indicative of proper placement of the needle. Synovial fluid often is not abundant and a given joint may contain relatively small quantities (0.1 to 2.0 cc.). If excessive fluid is present, it may be withdrawn in order to prevent dilution of the drug, although this is not always necessary. With the needle left in place, the aspiration syringe is detached and a second syringe containing the desired quantity of HYDROCORTONE Acetate is attached. The hormone then is injected gently, provided that tissue resistance is absent. With the needle still in place, the plunger may be moved in and out several times to assist in mixing the hormone with the synovial fluid. The needle then is withdrawn and a small sterile dressing placed over the site. The patient should be cautioned not to indulge in overactivity of the joint and to return for re-injection when the symptoms recur. The intervertebral joints should *not* be injected with HYDROCORTONE Acetate

Detailed information on intra-articular administration of HYDROCORTONE Acetate is available on request.

Dosage in Rheumatoid Arthritis and Osteoarthritis

The dose of HYDROCORTONE Acetate depends on the size of the joint and, to a lesser degree, on the relief obtained. The usual dose in a knee is 25 mg., increased to 37.5 mg. if the smaller dose produces insufficient or too transient therapeutic effect. Doses of more than 50 mg are not recommended. In smaller joints, 10 to 15 mg. may produce successful results

The patient should be cautioned against overactivity

of the joint. Repeated observation is necessary and re-injection should be made when symptoms recur. For continued effect, injections may be repeated at set intervals (usually once weekly). The degree and duration of relief from the first few injections should be observed before increasing the dose or re-injecting HYDROCORTONE Acetate. The length of remission depends somewhat on the particular joint involved. Severely inflamed joints must be injected every few days, while in other cases benefit is maintained for as long as eight or nine weeks. The relapse has never appeared worse than the pretreatment arthritic state in a series of cases studied.

Tolerance

HYDROCORTONE Acetate, administered intra-articularly in recommended dosage, exerts a purely local action, independent of systemic effects. No untoward effects have been observed in any of the cases studied.

SELECTED REFERENCES

[1] Hollander, J L., Brown, E M, Jr., Jessar, R. A., and Brown, C Y. *J.A M A* 147: 1629–1635, Dec 22, 1951
[2] Ziff, M, Scull, E., and Bunim, J. J.: *Federation Proc.* **11:** 405, March 1952.

ACUTE RHEUMATIC FEVER

The gratifying clinical effects produced by oral or parenteral treatment with CORTONE may hold new hope for patients with acute rheumatic fever. This disease constitutes a serious threat to health as well as life itself, especially among children and young adults More deaths are caused by rheumatic fever during the first two decades of life than by all the communicable diseases and pneumonia combined. Rheumatic fever is the cause of 93 per cent of all heart disease in patients under twenty years of age.

During World War II, more than 50 per cent of rejections for military service in the armed forces of the United States due to cardiovascular abnormalities were caused by rheumatic heart disease.

Barnes, *et al.*,[3] in discussing a series of rheumatic fever patients who received CORTONE, state their theory for the mode of action of the hormone as follows: ". . . acute rheumatic fever is a self-limiting disease, and the duration of the rheumatic state may be regarded as being determined either by disappearance of the sensitizing agent or, less likely, but possibly, by continuation of the peculiar reactions of the tissues of the host beyond the time of disappearance of the sensitizing agent."

In the reaction of sensitized cardiac tissues to such an agent, it can be assumed that there is first an exudative stage, followed by a proliferative stage, which in turn is followed by a reparative stage. In all probability the latter stage is responsible for permanent impairment of the heart. There exists evidence that CORTONE combats inflammatory reactions in mesenchymal tissue In addition, the action of CORTONE in suppressing the acute manifestations of rheumatic fever implies the suppression of the exudative inflammatory process in the heart. "If this assumption is correct, it is hoped that the proliferative and reparative stage of the disease will be forestalled."[3]

Clinical Response

Therapy with CORTONE *effectively suppresses the acute manifestations of rheumatic fever.* Within twenty-four hours after the initial administration of CORTONE, patients usually describe a sense of well-being and appear alert instead of "ill and toxic." Temperatures that have been elevated generally become normal within one to four and a half days. Appetites usually improve, with resultant true weight gains. In most instances, pa

inflamed joints become symptom-free, usually within the first week of treatment.

In many of the patients with acute rheumatic fever, improvement has been maintained following treatment. In the absence of chronicity, the symptoms disappear and remain absent if CORTONE is given long enough (three to twelve weeks). Other patients with acute rheumatic fever may relapse if the medication is discontinued, but respond promptly to re-instituted therapy, and may remain apparently well after discontinuance of the second or later courses of treatment. While CORTONE has demonstrated value in curtailing the acute manifestations of rheumatic fever, long-term studies will be necessary to evaluate its ability to prevent the development of chronic valvular lesions. Clinical experience "gives rise to considerable hope" that the early and adequate administration of CORTONE will prevent or markedly minimize permanent cardiac injury in the large majority of cases.[3]

Examination of the cardiovascular system reveals the following effects of CORTONE:

Pulse rate. Tachycardia, when present, disappears within five days after treatment is started. Bradycardia may accompany the use of CORTONE in some cases, particularly when high doses are given. It has been observed in young adults receiving 200 mg per day, but disappeared shortly [illegible]

rheumatic fever with CORTONE.

Electrocardiographic findings: In patients with prolonged P-R intervals, return to normal or almost normal limits usually occurs within eight days after the beginning of treatment. Electrocardiograms have shown no evidence of toxic effects on the heart.

The following reports illustrate the effect of CORTONE

in cases of first as well as recurrent attacks of acute rheumatic fever, with or without cardiac pathology.

Case A: [8]

RHEUMATIC FEVER—*First Attack, Without Previous Damage to the Heart Valves or Carditis.*

(CORTONE administered for 38 days)

Prior to Therapy with CORTONE—A 15-year-old girl was admitted to the hospital with ankles moderately swollen, warm, and tender (grade 2). There was pain on motion of the ankles, and the left elbow and right knee were very tender.

Temperature was 100 6° F ; pulse rate 112 per minute; blood pressure 126 mm. of mercury systolic and 80 diastolic The heart was not enlarged Murmurs were not heard, but the first and second heart sounds were poorly differentiated. On the day CORTONE was started, ankles and knees were so painful that voluntary motion was impossible, passive motion unbearable.

Response to CORTONE—The initial injection of 100 mg. of CORTONE was given March 28, 1949 A total of 4 65 Gm of the

[illegible]

tergren method) The P-R interval dropped from 0 24 sec to 0 16 sec. in ten days; heart rate from 112 to a rate slightly [illegible]

Gm. per 100 cc.

Withdrawal of CORTONE—After May 20, a rise in the sedi- [illegible]

normal.

The patient was dismissed from the hospital July 2, 1949.

Menses ceased during therapy, but resumed in mid-July.

Variable and intermittent heart murmurs were present during the hospitalization period, but none was heard at the time of dismissal. Nine months later, examination disclosed no cardiac murmurs and a teleroentgenogram revealed that the heart was normal in size and contour. The patient resumed the active life of a schoolgirl in September 1949.

Case B: [2]

RHEUMATIC FEVER—*First Attack, Without Previous Damage to the Heart Valves or Carditis.*

(CORTONE administered for 55 days.)

Prior to Therapy with CORTONE—Woman, age 24, was admitted to the hospital March 21, 1950, complaining of slight pain in the right knee. There was no personal or family history of rheumatic fever. Three weeks before admission she had had a severe sore throat. Slightly more than two weeks before admission polyarthritis began to appear.

Response to CORTONE—A dose of 200 mg was given intramuscularly on March 26, 1950. A total of 5.15 Gm. was given over a period of fifty-five days

one month, there probably would have been a sharp reappearance of acute manifestations of rheumatic fever.

Case C: [3]

RHEUMATIC FEVER—*Recurrent Attack, With Previous Carditis and Cardiac Dilatation and Failure.*

Prior to Therapy with CORTONE—The diagnosis in the case of this 13-year-old girl was acute rheumatic fever, carditis, and cardiac dilatation and failure. (A previous illness had been diagnosed as rheumatic fever.) From Jan 10 to Feb. 5, 1950, inclusive, treatment consisted of bed rest, salicylates, and digitalis This brought the temperature down, but heart rate and sedimentation rate remained well above normal.

Response to CORTONE—From Feb. 6 to Mar. 6, 1950, inclusive, the patient was given 100 mg of CORTONE daily, totaling 2 9 Gm in twenty-nine days.

Sedimentation rate declined to a more nearly normal figure by the time therapy with CORTONE was terminated Temperature, which showed an upward trend toward the end of the salicylate period, again was reduced by CORTONE. The heart rate dipped sharply during the middle of the treatment period, but rose thereafter.

The heart, which was markedly enlarged at the start of therapy with CORTONE, was found to be greatly reduced in size by March 6, when therapy was concluded This was paralleled by a decrease in venous pressure and by clinical improvement. The authors state that reduction in venous pressure and marked reduction in size of heart are regarded as a favorable response to CORTONE in this case of rheumatic carditis They state further that results might have been even better if the administration of CORTONE had been begun earlier in the course of the acute rheumatic fever.

Case D: [14]

RHEUMATIC FEVER—*Protracted Carditis, Cardiac Dilata-*

d
f

dence of acute rheumatic carditis, enlarged heart, and mitral

insufficiency, but no evidence of congestive failure. Clinical data revealed moderately elevated erythrocyte sedimentation rate, markedly depressed hemoglobin, prolonged P-R interval on the electrocardiogram, and marked prolongation of the electric systole (QTc.).

Protracted carditis continued for more than a year with evidence of progressive heart disease. Pulse rate was consistently elevated Although the temperature curve was flat, and the erythrocyte sedimentation rate was within normal limits, vital capacity was much below normal. The heart sounded active and his electric systole (QTc) was prolonged Fourteen months after admission, the patient developed acute appendicitis that was treated surgically. Following this, his condition became definitely worse Temperature, pulse rate, and erythrocyte sedimentation rate became appreciably elevated. He developed dyspnea, orthopnea, sacral and ankle edema. Mercurial therapy became necessary

Response to CORTONE—On July 25, 1950, two months after the marked recrudescence of rheumatic activity, therapy with CORTONE was begun, a total of 10 95 Gm. was administered over a period of 107 days The immediate response to CORTONE was dramatic The patient became more alert and more aware of [illegible]

[illegible] and there no longer was any evidence of [illegible]

Dosage in Acute Rheumatic Fever

(*See also* GENERAL CONSIDERATIONS, page 33)

The optimal dosage with CORTONE for the treatment of rheumatic fever has not yet been established. In order to achieve a prompt remission, adequate initial dosage is es-

sential. In most cases, satisfactory results have been obtained with the following:

1st day: Up to 400 mg. of CORTONE in divided doses.

2nd day, on: 200 mg. daily until a satisfactory response is obtained.

Then: Step-wise reduction to 100 mg., or less, daily maintenance dose, continued for four to eight weeks, or longer. Withdrawal should be gradual.

It is highly important that the natural history of the disease be considered and that re-treatment be instituted as indicated by signs and symptoms of reactivation of the disease. These include return of fever, increase in sedimentation rate, recurrence of arthralgia, and lengthening of the P-R interval.

SELECTED REFERENCES

[1] Barnes, A. R.: *Proc. Staff Mtgs., Mayo Clin.* 25: 478–479, Aug. 16, 1950.

BRONCHIAL ASTHMA

The Clinical Response

CORTONE, in adequate dosage, has proved highly effective in the treatment of severe asthma. Significant relief is experienced, often within five to twelve hours, even by patients with severe chronic intractable asthma that has become refractory to other forms of therapy. The administration of CORTONE in status asthmaticus in many instances produces relief of the symptoms in both children and adults. After administration of CORTONE to asthmatic patients, a significant increase in vital capacity, a feeling of well-being, and improved appetite have been observed, together with the symptomatic improvement.

Beneficial effects that can be achieved with CORTONE in certain cases of bronchial asthma are shown clearly in the following clinical reports These case histories also illustrate the feasibility and effectiveness of maintenance dosage:

Case A:

CHRONIC ASTHMATIC BRONCHITIS

Prior to Therapy with CORTONE—A 19-year-old girl had chronic asthmatic bronchitis and emphysema following pneumonia when she was 12. The condition progressed despite tonsillectomy and two years of antiallergic and other conventional treatment She had missed several weeks of school each year

Three years ago, examination revealed reduced vital capacity (1 3 liters), moderately pronounced pulmonary fibrosis, and early cylindrical bronchiectasis. Under continuous antibiotic [illegible]

tion. Severe cough and wheezy dyspnea developed within a few days Chest X-ray did not reveal complications such as pneu-

sential. In most cases, satisfactory results have been obtained with the following:

1st day: Up to 400 mg. of CORTONE in divided doses.

2nd day, on: 200 mg. daily until a satisfactory response is obtained.

Then: Step-wise reduction to 100 mg., or less, daily maintenance dose, continued for four to eight weeks, or longer. Withdrawal should be gradual.

It is highly important that the natural history of the disease be considered and that re-treatment be instituted as indicated by signs and symptoms of reactivation of the disease. These include return of fever, increase in sedimentation rate, recurrence of arthralgia, and lengthening of the P-R interval.

SELECTED REFERENCES

1 Barnes, A. R: *Proc. Staff Mtgs, Mayo Clin.* 25: 478–479, Aug 16, 1950.
2 Barnes, A R · *Circulation* 3: 770–775, May 1951
3 Barnes, A R., *et al: A.M.A. Am. J Dis. Child* 82: 397–425, October 1951.
4 Brewer, T F: *J Clin Endocrinol.* 11: 146–151, Feb. 1951.
5 Hansen, A. E: *J A.M.A* 148: 1481–1485, April 26, 1952.
6 Harris, T. N., Abrams, W. B, Leo, T. F P., and Hubbard, J. P · *Circulation* 3: 215–223, February 1951.
7 Kuttner, A. G, *et al · J.A.M.A.* 148: 628–634 Feb. 23, 1952.
8 Kuzell, W. C: *Stanford M Bull* 9: 119–131, May 1951.
9 McEwen, C, *et al.: Bull New York Acad. Med.* 26: 212–228, April 1950.
10 Rathbun, J C, McAlpine, H., and Manning, G W.: *Canad M.A J* 65: 113–115, August 1951.
11 Rawls, W. B, and Ancona, V C.: *New York State J. Med.* 51: 1625–1632, July 1, 1951.
12 Reich, N. E: *Am. Pract. & Digest of Treatment* 2: 328-331, April 1951.
13 Shetlar, M. R., *et al.: J. Lab. & Clin Med.* 39: 372–382, March 1952.
14 Taran, L. M.: Personal Communication.

Response to CORTONE—During a recurrence in September 1951, oral CORTONE was started with an initial daily dose of 150 mg. Antibiotic therapy was continued as before.

Within forty-eight hours the patient started to expectorate a large amount of purulent phlegm. Cough and dyspnea disappeared completely. The vital capacity increased from an original 1 8 liters to 2 8 liters. She felt "better than ever before."

After a daily dose of 100 mg of CORTONE had been given for two weeks, this treatment was discontinued for two weeks. Res- [illegible]

A second bronchography revealed that the formerly dilated bronchial segments had decreased considerably in caliber, and less bronchial obstruction was obvious.

Case C. [2]

SEVERE SEASONAL ASTHMA

Prior to Therapy with CORTONE—Male, aged 48, had severe seasonal asthma since he was eighteen and hay fever since the age of nine. After successful pollen desensitization for several years, intractable asthma recurred so severely that the patient had to be taken to work in a warm car In desperation, he contemplated moving to a warm climate, but this was impracticable.

Response to CORTONE—Therapy with CORTONE consisted of [illegible]

be cautioned against overexertion.

After three weeks, an attempt was made to stop CORTONE, but coughing and wheezing occurred within six days. Since then, the patient has remained practically symptom-free on 50 mg. of

monia or atelectasis. Despite high doses of various antibiotics, epinephrine, aminophylline, and other drugs, the patient's condition developed into status asthmaticus.

Response to CORTONE—*No hospital space was available and* oral therapy with CORTONE was started at home with initial doses of 50 mg. four times a day. Antibiotics were continued as before.

Six hours after the first dose of CORTONE, the respiratory symptoms began to improve, and six hours later had subsided to a great extent. Dosage of 200 mg. of CORTONE per day was continued for two days more and then was reduced gradually to 50 mg. On the third day following therapy with CORTONE, the condition had improved so much that the patient was able to go to her doctor's office.

At that time, little wheezing was noticeable, and the vital capacity was 1 8 liters, as it had been shortly before the asthmatic attack. The patient's general condition also had improved remarkably. After one week's convalescence, she went back to [illegible] 75 mg. of [illegible] addition to anti- [illegible] occasionally had [illegible] s condition has [illegible]

Case B: [6]

SEVERE ASTHMATIC BRONCHITIS

Prior to Therapy with CORTONE—A 20-year-old girl had severe asthmatic bronchitis, apparently originating from an attack of pneumonia when she was 12. The condition was aggravated by another attack of pneumonia when she was 17. Prolonged [illegible]

of antibiotics decreased [illegible] several milder ones occurred.

first day or two may be necessary. Thereafter, dosage is tapered off to a maintenance level or gradually discontinued.

CORTONE, combined with hyposensitization, has been observed to produce much greater relief in patients with *hay fever* than that obtained with measures used previously. During the height of the hay fever season, 25 mg. of CORTONE four times daily has been used successfully.[14]

SELECTED REFERENCES

Bronchial Asthma and Hay Fever

[1] Baldwin, H S., and deGara, P. F.: *J. Allergy* 23: 15–26 January 1952.

[2] Blumenthal, J. S : *Journal-Lancet* 71: 473–481, November 1951.

[3] Carey, R. A., Harvey, A. M , Howard, J. E , and Winkenwerder, W L *Bull. Johns Hopkins Hosp* 87: 387–414, November 1950.

[4] Carryer, H M , *et al* *J. Allergy* 21: 282–287, July 1950

[5] Cotton, A. L. *N. Orleans M. & Surg J* 103: 524–529, June 1951

[6] Finke, W.. Personal Communication

[7] Franklin, W , Lowell, F C , Schiller, I. W , and Beale, [illegible]

June 1952.

[11] Prickman, L. E., *et al* : *A.M.A Arch. Surg.* 63: 647–651, November 1951.

[12] Schwartz, E *J.A.M.A* 147: 1734–1737, Dec. 29, 1951.

[13] Schwartz, E.: *J Allergy* 22: 1–3, January 1951.

[14] Schwartz, E , *et al* : *J. Allergy* 23: 32–38, January 1952.

CORTONE orally, per day, except when he exerts himself in cold weather. When the weather becomes warmer, it probably will be possible to discontinue medication.

Administration and Dosage in Bronchial Asthma, Status Asthmaticus, Hay Fever

(*See also* GENERAL CONSIDERATIONS, page 33)

In bronchial asthma, somewhat larger doses than those tabulated below may be required initially, and adequate initial dosage is essential in order to achieve prompt remission.

The necessary duration of treatment usually is not more than one to two weeks when the allergen is known and can be guarded against, *e.g.*, in seasonal allergy. However, in chronic intractable asthma due to unknown or uncontrollable causes, prolonged maintenance doses or repetition of the original regimen may be required. The duration of improvement varies greatly, depending in part on whether the causative agent can be avoided.

There should be strict supervision of the patient during therapy with CORTONE, and the use of antibiotics and other appropriate measures for intercurrent infections is essential. When required, conventional antiasthmatic therapy should be continued until the effect of CORTONE makes its use unnecessary. (*See also* page 6.)

Average dosage in chronic intractable cases of *bronchial asthma* is:

1st day—200 to 300 mg.

2nd day—100 to 200 mg.

3rd day—100 mg , *then,* reduce gradually to

Maintenance dose—usually 25 mg twice daily. (Patients frequently may be maintained for long periods on continuous dosage regimens of 50 to 100 mg daily.)

In *status asthmaticus*, as much as 300 mg. daily for the

inflammation, whether bacterial, anaphylactic, allergic, or traumatic in origin, and inhibits fibroblastic formation during tissue repair. Investigators have stated that the effectiveness of this blocking action is unequaled by any previously available agent. While this therapy does not appear to influence significantly the underlying cause of the lesion, permanent impairment of vision may be prevented, since the physician gains time to identify the underlying cause and to institute specific corrective measures.

In general, the best results with CORTONE in eye diseases are obtained in inflammatory conditions, with acute lesions more favorably influenced than chronic ones. CORTONE is used to greatest advantage in (*a*) *self-limited* disorders such as nongranulomatous iritis, allergic keratitis, and the like, in which the destructive phases of the disease may be aborted by prompt therapy with CORTONE; (*b*) in *chronic* ocular conditions, when the inflammatory and exudative phases threaten the functional integrity of the eye. In the latter type, specific antimicrobial therapy should be used, whenever necessary, while CORTONE is helping to preserve the functional integrity of the eye. (*See also* page 8)

Relapses after adequate therapy with CORTONE are relatively uncommon in self-limited conditions. Relapses may occur in chronic active lesions, but re-treatment usually results in improvement.

For the most part, hereditary and degenerative eye diseases do not show appreciable response to therapy with CORTONE. Further study is necessary to evaluate the role of CORTONE, administered parenterally or orally, in a variety of other lesions such as retrolental fibroplasia in its early stages, hemorrhagic retinitis, and exudative retinitis (Coats's disease). Some clinical evidence suggests that CORTONE may delay the healing of an open, acute corneal lesion. However, it does not interfere with epithelial

INFLAMMATORY EYE DISEASES

The destruction of vision which may result from inflammatory eye diseases often is preventable by therapy with CORTONE. By reducing the development of corneal scarring and vascularization, CORTONE, in many instances, prevents partial or total blindness.

Even when vision is not threatened, prolonged disability may be avoided, and many patients can continue their daily activities after administration of CORTONE. Moreover, cases refractory to other forms of treatment frequently have shown prompt improvement after therapy with CORTONE.

In addition to its helpful effect in diseases confined to the eyes, CORTONE has been distinctly beneficial in the *treatment of ocular manifestations accompanying certain* systemic diseases, such as rheumatoid arthritis and allied conditions, sarcoidosis, scleroderma, dermatomyositis, periarteritis nodosa, and disseminated lupus erythematosus (Note, for example, that uveitis accompanies rheumatoid arthritis in from 2 to 5 per cent of cases; approximately 20 per cent of children with Still's disease, and from 15 to 50 per cent of patients with Marie-Strumpell disease may develop uveitis.)

The Clinical Response

CORTONE appears to interfere with, or alter, certain tissue responses to injury. In a number of ocular conditions, such as anterior uveitis, excessive reaction rather than direct injury is recognized as being the dangerous factor. CORTONE seems to create a protective "barrier" between the disease process and the ocular tissues.

In the initial acute phase of ocular inflammation, appropriate systemic or local therapy with CORTONE rapidly provides symptomatic relief. Moreover, it frequently accomplishes temporary control of the exudative phases of

Sensitivity of a patient to his own uveal tract pigment is believed by some authorities to play a role in the pathogenesis of *sympathetic ophthalmia*. Vision can be saved in this self-limited disease if the inflammatory reaction can be controlled, and such control may be achieved by therapy with CORTONE. Sympathetic ophthalmia may follow a penetrating traumatic or surgical wound which involves the uveal tract. In this disease, uveitis develops in the second eye, usually after from two to ten weeks, occasionally after several years. The subsequent clinical course is the same in both eyes. If left untreated, blindness generally results in from six to twelve months; a few patients suffer only impaired vision.[10]

Allergic conjunctivitis in an acute or chronic catarrhal form usually is part of a larger allergic syndrome. Acute conjunctivitis often is associated with contact dermatitis of the eyelids which may be due to drug allergies, or it may occur alone and be caused by direct contact with airborne substances such as pollen, spores of fungi, dust, or animal danders.

Case B:[11]

ALLERGIC CONJUNCTIVITIS

Twelve days later, a flare-up, again involving the right eye,

regeneration. Moreover, it has been observed that when such a lesion heals during antibiotic therapy, CORTONE, topically applied, reduces the ordinarily expected scarring and vascularization.

Therapy with CORTONE is of benefit in many previously intractable ophthalmic conditions, especially those *resulting from* anaphylactic or allergic *reactions*,[17] *including* those caused by chemical irritants.

Hypersensitivity is believed to play a causative role, not only in allergic conjunctivitis, but also in the inflammatory reaction in such eye diseases as nongranulomatous iritis, sympathetic ophthalmia, vernal conjunctivitis, and the inflammatory changes associated with herpes zoster ophthalmicus.

Clinical experience with CORTONE in various ophthalmic conditions—allergic as well as nonallergic—is described below

Nongranulomatous iritis is believed to be an allergic reaction dependent on bacterial hypersensitivity. This condition is usually associated with rheumatoid arthritis or follows some infectious process Attacks, lasting from a week to several months, usually are self-limited. Unless there are repeated attacks, the eye generally clears without residual effects, however, there is a definite tendency to such recurrences. Therapy with CORTONE controls all symptoms with amazing rapidity when the disease is characterized by ciliary congestion, edema of the iris, and protein and cellular exudate in the aqueous [24]

Case A:[10]
NONGRANULOMATOUS IRITIS

patient was advised to continue using CORTONE at home three times daily to prevent recurrence

Ophthalmic herpes zoster—accompanied sometimes by multiple eye involvements including deep keratitis, iritis, and iridocyclitis—may result in blindness or greatly reduced vision in severe cases. CORTONE has been found a valuable adjunct to antibiotics and other measures used during the treatment of this condition

In two cases of ophthalmic herpes zoster, dramatic improvement of the inflammatory signs was brought about in one day by the local instillation of CORTONE, 1 drop every hour. A recurrence followed discontinuance of therapy with CORTONE, but the inflammatory reaction responded promptly when the instillation of CORTONE was resumed.[10]

The following case reports illustrate results obtained with CORTONE in optic neuritis, chemical burn, and corneal injury.

Case E: [14]

OPTIC NEURITIS

[illegible]

acute optic neuritis; a study of the visual fields revealed a relative scotoma

Treatment was begun locally with CORTONE (drops) four times a day, and intramuscular dosage of 50 mg A nose and throat consultation was requested, but was not obtained for three days. In the meantime, there was a marked reduction of the papillitis and improvement, by January 10, to vision of 20/30 to 20/25.

[illegible]

improved rapidly when 2 drops of CORTONE were instilled hourly In three days the eye was clear and CORTONE was discontinued after another two days of therapy.

Vernal conjunctivitis, a rather rare chronic inflammation producing characteristic changes in the conjunctiva, is another ocular condition in which therapy with CORTONE has been helpful.

Case C: [10]

VERNAL CONJUNCTIVITIS

An 18-year-old boy had severe bilateral vernal conjunctivitis with huge follicles in the palpebral conjunctiva and vascularization and infiltration of the cornea A total of 700 mg of CORTONE was given parenterally over a three-day period. There was a significant drop in the blood eosinophil count. Following the local instillation of CORTONE (1 drop per hour during the day for two weeks) the follicles diminished in size, the cornea cleared, and vision improved from 20/100 to 20/40.

Case D. [3]

VERNAL CONJUNCTIVITIS

Woman, age 42, had burning, itching, and ropy secretion from eyes for the past 15 months She had been treated by several

Administration and Dosage in Eye Diseases Topically or Systemically

CORTONE may be administered topically or systemically, depending on the nature and location of the disease process. In general, it seems advisable to use the topical mode of administration for inflammatory lesions of the anterior segment of the eye, and to reserve systemic administration for diseases of the deeper structures or for conditions that fail to respond satisfactorily to CORTONE applied topically. Mydriatics, miotics, or antibiotics, when indicated, should be used in addition to CORTONE[16] (*See also,* page 8.)

ADMINISTRATION (TOPICALLY)

Administered topically in recommended dosage, CORTONE (ophthalmic suspension or ointment) is very economical, much less of the hormone being required than in systemic administration. Effective therapeutic concentrations are achieved readily without producing undesirable systemic effects, or harmful effects on the ocular tissues, even on prolonged administration. No contraindications to the topical use of CORTONE have been noted, with the exception of ocular tuberculosis. Topical administration of CORTONE also can be used in aged and debilitated patients

CORTONE, applied topically, appears to benefit principally disorders of the anterior segment of the eye—the cornea and anterior uvea—and also has proved to be of great value in preventing relapse in patients with severe chronic iritis treated initially with oral or parenteral forms of CORTONE The topical use of CORTONE in certain corneal lesions is reported to have the additional advantage of promptly relieving pain and photophobia.

While topical administration of CORTONE is preferred in the treatment of inflammatory lesions of the anterior segment of the eye (*See* TABLE, page 66) oral or parenteral

Case F: [3]

CHEMICAL BURN

Left eye was burned severely with scrubbing solution. Examination revealed a superficial burn on the lower third of the cornea and bulbar conjunctiva. After the secretion was cleaned from the fornix, the entire area stained with fluorescein dye, indicating complete destruction of epithelium and involvement of stroma in this area.

The patient was admitted to the hospital Warm irrigations were given hourly, followed by instillation of CORTONE (drops) every hour This was supplemented by the use of 1 per cent atropine ointment three times daily and ointment of CORTONE every three hours After two days, the burned area was covered with fresh epithelium, and after eight days, the cornea and conjunctiva were completely epithelized. There was no stain with fluorescein.

The interval of instillation of CORTONE was reduced to every two hours, atropine was discontinued, and ointment of CORTONE was used at bedtime After 21 days, the cornea still was healed There was minimal scarring from the alkali burn At the end of 35 days, the eye was completely free from inflammation, slight haziness of superficial layers of the stroma were seen with slit lamp, and corrected vision was normal.

Case G: [14]

CORNEAL INJURY

A 41-year-old man was seen first September 18, 1950, with a severe laceration and abrasion of the cornea, left eye Despite all usual antiseptic, anesthetic, and cycloplegic medication, severe pain continued. On October 18, the unhealed cornea became severely infiltrated with a dirty, gray-yellow triangular ulceration.

On October 20, all anesthetic medication was discontinued and CORTONE was instilled every hour in the left eye Within three hours, the eye was comfortable for the first time in several weeks, and the patient could rest without sedatives

The ulcer healed in two weeks Only a small vascularized scar remained in the lower temporal quadrant of the cornea at the site of the deepest injury.

SAFETY

As only a relatively small amount is absorbed when CORTONE is applied topically, it is not necessary to observe patients for evidence of systemic effect. Moreover, when used as directed, prolonged topical administration of CORTONE has *produced no evidence of harmful effects on ocular tissues.*

ADMINISTRATION (SYSTEMICALLY)

CORTONE given orally or parenterally appears to affect all tissues of the eye, including the cornea and the anterior and posterior uvea. The systemic administration of CORTONE is required for the treatment of diseases that affect the deep ocular structures, and is advisable for initial prompt control of the more serious acute anterior lesions. There is clearing of the circumcorneal injection, clearing of vitreous exudates, circumscription of choroidal exudates, and disappearance of subretinal edema.

Numerous *acute* inflammatory diseases have been benefited by the parenteral or oral administration of CORTONE. (*See* TABLE, page 66). In regard to *chronic* eye diseases, CORTONE has demonstrated its usefulness in chronic iritis. Excellent results have been observed in such disorders, especially when topical application is employed following the course of parenteral or oral treatment.

DOSAGE (SYSTEMICALLY)

(*See also* GENERAL CONSIDERATIONS, page 33)

In general, dosage recommended for systemic therapy is similar to that described for rheumatoid arthritis.

Duration of treatment varies with the type of lesion, and should extend from a few days to several weeks, as necessary Iritis and retinitis centralis usually respond within three to five days. Optic neuritis (including retrobulbar neuritis), choroiditis, and chorioretinitis require somewhat longer periods, while sympathetic ophthalmia may require as long as three weeks of therapy.

use of the hormone also has proved effective in these conditions.

It has been suggested by Agatson[1] that CORTONE, applied topically for two or three days, often may be a useful diagnostic and therapeutic test, *e.g.*, to differentiate allergic from nonallergic conjunctivitis.

DOSAGE (TOPICALLY)

Two concentrations of ophthalmic suspension for topical use are available: 0.5 per cent and 2.5 per cent. The choice between these is dependent on the severity of the inflammatory reaction as well as on the type of disease present.

Where the inflammatory reaction is severe, treatment should be initiated with the 2.5 per cent concentration of the ophthalmic suspension, in order to bring the disease under control as rapidly as possible. Maintenance therapy then may be continued with the 0.5 per cent suspension if desired. In less severe cases, treatment may be instituted and continued with the 0.5 per cent concentration.

One or two drops of OPHTHALMIC SUSPENSION OF CORTONE ACETATE are placed in the conjunctival sac every hour during the day and every two hours during the night for the first two days. When a favorable response is obtained, the dosage may be reduced to one drop every four hours, and later to the same amount instilled three or four times daily for maintenance.

Also available is OPHTHALMIC OINTMENT OF CORTONE ACETATE, 1.5 per cent. In cases where an eye pad is used, the ointment—applied three or four times a day—may be more convenient than the suspension. The ointment may be preferable in conditions requiring more prolonged contact of CORTONE with tissues. In some instances, it may be desirable to use the ophthalmic suspension during the day, and to apply the ointment at bedtime, thus allowing the patient an uninterrupted night's rest.

[1] Agatson, H.: *Am J. Ophth.* 34: 1655–1664, Dec. 1951

[2] Breffeilh, L. A.. *N. Orleans M. & S. J.* 104: 321–326, February 1952.

[3] Clark, W. B : Personal Communication.

[4] Crane, G. W., Jr., and McPherson, S D, Jr.: *Am J. Syph, Gonor. & Ven. Dis* 35: 525–531, November 1951 [*Interstitial keratitis.*]

[5] Duke-Elder, S · *Brit. J. Ophth.* 35: 637–671, Nov. 1951

[6] [illegible]

[7] [illegible]

[8] [illegible]

[9] Hanser, S. A : *Trans Am Acad. Ophth. & Otolaryngol.* 56: 256–266.

[10] Harvey, A M., Howard, J. E., and Kattus, A. A.: *Bull. Johns Hopkins Hosp* 87: 461–481, November 1950

[11] Hoch, S M : Personal Communication.

[12] Jensen, C D F., and Ward, J. F : *Northwest Med.* 50: 36–38, January 1951.

[13] King, C, Lewis, P., and McKinney, W.: *J Tennessee S.M.A.* 45: 5–9, January 1952

[14] Luedde, W. H , and Luedde, P S . Personal Communication.

[15] Posner, A *Eye, Ear, Nose & Throat Monthly* 29: 316–317, 331, June 1950. [Iritis]

[16] Purnell, J E , and Leopold, I. H *Am. J Ophth.* 35: 663–670, May 1952.

[17] Scheie, H G , Tyner, G. S., Buesseler, J. A., and Alfano, J E *A.M.A. Arch Ophth* 45: 301–316, March 1951

[18] Spies, T D, and Stone, R. E.: *South M J.* 43: 871–874, October 1950 [Iritis; Uveitis]

[19] Steffensen, E H., *et al.*: *Am. J. Ophth* 34: 345–356, March 1951.

[20] Stillerman, M. L.: *A.M.A. Arch. Ophth.* 45: 239–250, March 1951.

[21] Theodore, F. H.: *Eye, Ear, Nose & Throat Monthly* 29: 314–315, June 1950. [*Uveitis*]

[22] Thygeson, P , and Fritz, M H.: *Am. J. Ophth.* 34: 357–360, March 1951. [illegible]

23 [illegible]

24 [illegible]

25 [illegible]

Administration of CORTONE *In Various Eye Diseases*

Topically	*Systemically*
Preferable in inflammatory lesions of anterior segment of the eye, although oral or parenteral administration also is effective.	Parenterally or Orally—generally advisable for diseases of deeper ocular structures and for those conditions that fail to respond satisfactorily to topical administration.
OPHTHALMIC SUSPENSION OR OINTMENT:	PARENTERAL SUSPENSION, OR TABLETS FOR ORAL USE:
Nonspecific superficial keratitis Deep keratitis Acne rosacea keratitis Ophthalmic herpes zoster Sclerokeratitis Phlyctenular keratoconjunctivitis Allergic conjunctivitis Vernal conjunctivitis Chronic conjunctivitis (antibiotics also may be required) Acute iritis Chronic iritis (topical therapy especially effective after initial course of CORTONE given systemically) Recurrent marginal ulceration	Iritis and iridocyclitis Chorioretinitis Nonspecific choroiditis or uveitis Retinitis centralis Ophthalmic herpes zoster Optic neuritis, including retrobulbar neuritis Sympathetic ophthalmia Uveitis following surgery (As result of successful treatment, the secondary glaucoma that often complicates some of these conditions may be minimized or avoided, rarely, the secondary glaucoma may become aggravated during treatment with CORTONE)

the skin. The photographs (*Plate* XVIII) show the progress made in the first eight days.

The amount of CORTONE was reduced gradually until the maintenance dose was found to be 12.5 mg. every day to every other day. When the dermatitis was under control this dosage was continued for several months Pigmentation increased as dosage was increased. While being treated with CORTONE, the patient was able to tolerate certain topical medications that also were beneficial to the dermatitis.

Case B:[24]

ATOPIC DERMATITIS

A man, age 34, was admitted to the hospital with a severely pruritic atopic dermatitis A generalized acute erythematous [illegible] Some [illegible]

was cortisone.

Therapy with CORTONE was begun orally with 100 mg twice daily for eight days A total of 1,600 mg was given CORTONE relieved the pruritus rapidly and, within a few days, the erythema and associated edema improved. The weeping and excoriated areas healed promptly (*See* ILLUSTRATIONS, *Plate* XV)

Equally outstanding results have been obtained with CORTONE in the treatment of atopic dermatitis that sometimes occurs following the use of an antibiotic. The use of CORTONE in atopic dermatitis has been suggested for the control of severe acute exacerbations of a relatively stationary eruption, or to permit conventional forms of therapy to become effective once more. It is reported that very small maintenance doses of CORTONE (*e g.*, 25 mg. daily) sometimes are warranted for extended periods of time to prevent eruption and itching in otherwise intractable cases of atopic dermatitis[1]

The following case history of a patient with *exfoliative dermatitis* demonstrates the beneficial effects obtained by therapy with CORTONE.

SKIN CONDITIONS

Therapy with CORTONE has proved highly beneficial in many dermatologic conditions—allergic or nonallergic.

Allergic Skin Conditions

The Clinical Response

Among the allergic dermatoses that have shown dramatic response to CORTONE administered orally or parenterally, are angioneurotic edema, atopic dermatitis, rhus (poison ivy) dermatitis, and exfoliative dermatitis, including cases resulting from drug allergy. CORTONE not only has relieved patients from the distressing and unsightly manifestations of many dermatologic conditions, but in some cases, such as severe exfoliative dermatitis, it has served to prevent a probably fatal outcome.

In serious pruritic and inflammatory phases of allergic eczematous contact-type dermatitis, the use of CORTONE has been recommended for symptomatic relief. In *atopic dermatitis,* response may be striking Itching subsides or becomes less severe within a few hours after administration of the hormone, eruptions that may have been present for many years may regress partially or completely within a few days.

Case A: [24]

ATOPIC DERMATITIS

A 35-year-old woman presented a typical atopic dermatitis of more than ten years' duration The face, neck, upper chest, antecubital ... were erythematous and ... evidence of scratching
Followin, ...)0 mg. a day, there was ... ıprovement ın

eczematization of the inguinal and perianal regions; generalized urticaria and angioneurotic edema of the face and hands; and pronounced swelling and tenderness of the wrists and elbows. The patient had a temperature of 103° F., and complained of pains in the joints.

Case E: [10]

DRUG REACTION

A 29-year-old man had developed exfoliative dermatitis and hepatitis during treatment with an antiepileptic drug. An attempt then was made to control his epilepsy with bromides In less than three weeks the patient developed chills, a temperature of 104° F, and a skin rash Despite withdrawal of bromides, he again developed exfoliative dermatitis, this time associated with pneumonia, asthma, and coma He was treated with CORTONE for eleven days, the dosage ranging from 300 to 150 mg per day during the first four days; 100 mg. per day for the next five days, and 50 mg. on each of the last two days of treatment. An almost immediate drop in the temperature to a

exfoliative dermatitis, it was the clinical impression that the recurrence during which he was desperately ill was indeed arrested by therapy with CORTONE (*See* ILLUSTRATIONS, *Plate* XXI.)

Case F: [21]

DRUG REACTION

Man, age 40, developed generalized erythroderma following gold therapy for arthritis. Seborrhea-like dermatitis of the scalp and all the intertriginous areas spread rapidly over the entire body The flexural surfaces were edematous and weeping A course of British anti-lewisite (BAL) brought no improvement.

Case C: [22]

EXFOLIATIVE DERMATITIS

A 78-year-old man had an intense universal exfoliative dermatitis for two years that resulted in intolerable pruritus. He was emaciated and bedridden. There was pronounced lymphadenopathy and anemia, lymphoblastoma was excluded by blood and biopsy studies He had suffered from asthma and allergic reactions to topical therapy.

After four weeks of symptomatic care in the hospital, his anemia improved, but his skin and mental condition deteriorated.

CORTONE, 1.1 Gm, was given in 12 days. Twelve hours after the first injection, the skin appeared less red; in three days, the infiltration, scaling, and pruritus were greatly diminished. Pruritus and desquamation ceased in 12 days, but the skin remained pink and thickened. Two deep lacerations, which the patient had on the forehead, healed promptly. The patient was able to leave his bed An asymptomatic drop in serum carbon dioxide to 22 milliequivalents per liter was noted. Five days after the last injection of CORTONE, the pruritus, erythema, and exfoliation recurred.

A second course of CORTONE, 0.8 Gm., was used over an eight-day period, and improvement was even more noticeable than previously A partial relapse occurred three weeks later while the patient was receiving maintenance therapy of 100 mg biweekly. This was relieved by a 200-mg injection of CORTONE followed by 200 mg. biweekly. After the patient was discharged from the hospital, remission was maintained by 200 mg triweekly for two months (Total dosage of CORTONE used in this case was 8 0 Gm. given over a period of 130 days.)

Remarkable improvement was obtained with CORTONE in the following dermatologic disturbances, resulting from *hypersensitivity to drugs or other allergens:*

Case D: [21]

DRUG REACTION

A patient, age 37, received injections of penicillin for three days Ten days later he noted severe itching of the scrotum and inguinal regions The following day there was pronounced edema and erythema of the scrotum, erythema, scaling, and

six hours after onset of the dermatitis. Children up to five years of age were given 25 mg. a day orally, one-quarter tablet four times a day. (Now that 5-mg. tablets are available, more [illegible]

salt diet. Duration of dosage for all averaged four days. In two cases with very severe generalized dermatitis, a higher initial dosage was used

Two children showed fatigue No other reactions were noted, and there was no instance of secondary infection in this series.

Fourteen children were relieved of pruritus in twenty-four hours In eighteen, there was rapid drying of lesions under therapy. "Six of the children in this series were known hypersensitive types and had had repeated episodes of poison ivy each season; it was the opinion of the parents that the addition of cortisone to the early therapeutic regimen was of real value."

Nonallergic Skin Conditions

The Clinical Response

CORTONE is an extremely valuable and sometimes lifesaving agent in selected cases of serious nonallergic skin diseases that are notoriously refractory to other measures. Among these conditions are pemphigus, scleroderma, and dermatomyositis.

Until the advent of CORTONE, many patients with *pemphigus* were either doomed to death or to incapacitation CORTONE has been credited with saving the lives of patients with malignant pemphigus. Use of CORTONE also has made it more simple and less expensive to manage patients, some of whom now can be treated at home without the necessity of prolonged hospitalization and nursing service. Formerly, hospitalization was necessary for all but those patients with the most benign forms of the disease.

Results with CORTONE in pemphigus are variable, but in many instances have been impressive. It has been

Two weeks later, 100 mg. of CORTONE were injected daily for six days, with prompt involution. Then, 50 mg. were injected daily for five days. One week later, mild recurrence of the seborrhea-like dermatitis was controlled with 50 mg. of CORTONE orally per day for three weeks.

Case G:[18]

EXFOLIATIVE DERMATITIS DUE TO CONTACT ALLERGEN

A 59-year-old man was hospitalized because of a generalized exfoliative erythroderma attributed to a contact allergen. In addition to the skin involvement, there was marked loss of hair and diminished sweating.

CORTONE was administered both intramuscularly and orally starting with 200 mg. daily. After four days the amount was reduced to 100 mg. daily and this was continued for three months. Total dosage was 10.6 Gm. The symptomatic relief from itching was prompt. There was an excellent regrowth of hair, marked clearing of the skin, and return of sweating.

Patients with *angioneurotic edema* have obtained symptomatic relief through CORTONE; during treatment, the lesions may be partially or completely suppressed.

In all cases of allergy it is important not to overlook conventional management. The cause of the allergy should be investigated and eliminated if possible in order to prevent relapse.

Poison ivy dermatitis[6] with severe involvement about the face and eyes has promptly responded to oral therapy with CORTONE. Relief of pruritus and subsidence of the edema and exudation have been produced in cases that have been intractable to other measures. In general, treatment is necessary for only a few days.

In an experimental series,[15] CORTONE was used to determine its value in *early* cases of *noninfected* poison ivy dermatitis. Twenty-one children, three to twelve years of age, were included. Wet dressings and a simple talc paste were the only local medications used.

Treatment with CORTONE was begun twenty-four to thirty-

phigus, lesions of the oral mucous membranes are more resistant to treatment than are those of the skin [14]

Additional experience with CORTONE in the treatment of pemphigus is presented in the following case reports.

Case A: [24]

PEMPHIGUS VULGARIS

A 32-year-old woman was hospitalized Sept. 11, 1950, for treatment of *pemphigus vulgaris* of two months' duration Vesicular and bullous lesions were scattered over the face, chest, abdomen, back, and axillae The scalp presented denuded, moist areas with alopecia and crusting. Raw, denuded areas were noted on the buccal and vaginal mucosa, and in the perianal area.

Thirteen days of treatment with corticotropin up to 200 mg. a day, caused some improvement This drug was discontinued because of marked fluid retention. After a short interval, CORTONE was started orally.

The initial dose of 300 mg a day was gradually reduced as improvement was noted The effectiveness of CORTONE was enhanced by the intravenous administration of suramin sodium The patient was much improved when she was discharged from the hospital on Nov. 16, 1950 She had received a total of 5,700 mg of CORTONE in seven weeks CORTONE was continued at 50 mg a day and finally reduced to 25 mg It was discontinued the last week of January 1951. The patient has remained well since that time and is free from lesions.

Case B: [24]

PEMPHIGUS FOLIACEUS

A 75-year-old man gave a history of an eruption that started on the back of his neck in 1945. It had spread slowly to involve all other parts of the body When he was hospitalized August 17, 1950, he presented a generalized *pemphigus foliaceus* The extent and degree of involvement resembled an exfoliative dermatitis with moist as well as dry crusting and intervening denuded and raw areas.

Starting October 27, 1950, CORTONE was administered intramuscularly, 100 mg, twice daily. On November 9, 1950, the

claimed that CORTONE has a definite effect, however temporary it may be, on the course of all forms of this disease.[14] Some patients have enjoyed remissions throughout the treatment period. Others have remained in remission for weeks after the hormone was withdrawn. When sufficient amounts of CORTONE are used, much greater improvement in skin condition and general health has been achieved than with former modes of therapy; it is reported that the temperature becomes normal and a sense of well-being develops within twenty-four to forty-eight hours. Prompt diminution in vesiculation and a cessation of new cutaneous lesions have been observed after CORTONE was given for about one week.

As treatment continues, it may be necessary to increase the dosage in order to prevent relapse, but one group of investigators encountered no serious side effects despite the large doses of CORTONE used[8] The usual strict supervision of the patient should be observed during therapy with CORTONE. Small daily maintenance doses sometimes have produced adequate control

Remission lasting for five weeks was effected in a patient with *benign bullous pemphigus.* In this case, CORTONE was injected intramuscularly for thirty-three days in daily doses of 300 and 400 mg.[14]

In *benign exfoliative pemphigus,* approximately the same dosage of CORTONE is employed as in malignant pemphigus or benign bullous pemphigus. Improvement has been less rapid and less sustained than in other forms of pemphigus, but with adequate dosage of CORTONE given over long enough periods, satisfactory resolution of lesions has been produced.[14]

A patient with *malignant pemphigus* was given from 300 to 400 mg of CORTONE orally per day, totaling 5.7 Gm in twenty-three days. Remission lasted five weeks. Some mucosal erosions persisted, but in malignant pem-

CORTONE are far greater than with any agent yet used. Sense of well-being, appetite, and strength have increased, pain, soreness, and discomfort have disappeared or were greatly lessened. The characteristic abnormal collagen pattern appears to be altered, although the fundamental course is unchanged[26] Definite remissions of symptoms have lasted for varying periods of time and, upon their recurrence, administration of the hormone appears to bring about the same degree of improvement faster and with a smaller total dose than that required in previous courses of therapy.[18]

The symptomatic improvement which may occur when CORTONE is administered in scleroderma is exemplified in the following case report:

Case D:[26]

SCLERODERMA

A woman had diffuse scleroderma involving the skin, lungs, and the esophagus. Prior to therapy with CORTONE, the disease had progressed steadily, despite all therapeutic efforts

When CORTONE was used, the following beneficial effects were noted The skin became softer and more pliable, although

Of the side effects due to CORTONE, rounding of the face, acne, and water retention were quite pronounced. Medication with

dose was reduced to 100 mg. once daily. The patient was discharged from the hospital on this dose. The drug was well tolerated despite arteriosclerotic heart disease and an old fibrosis of the lung following tuberculosis. *See* ILLUSTRATIONS, *Plate* XXV, showing improvement following two weeks' treatment with CORTONE.

Case C: [3]

PEMPHIGUS VEGETANS

A man, age 42, with *pemphigus vegetans*, had been afflicted for the past four years with recurrent bullous lesions on the penis, umbilicus, and paronychial folds. For two years, severe bullous, eroded, and vegetated lesions had developed in the groins, axillas, intergluteal fold, mouth, and rectum. And for some months, scattered bullous lesions had been present on the scalp, trunk, and extremities. Any movement caused unbearable pain in the raw intertriginous areas, and the patient was bedridden There was a weight loss of 34 pounds.

Large bullae then broke out all over the face. These cleared gradually, but the patient's condition slowly worsened, and the downhill course became rapid two weeks before re-admission to a hospital The man was depressed and lost hope. At this time his back was covered with bullae. Nikolsky's sign was strongly positive, the mouth was so raw that eating was almost impossible, fluid was exuding freely from the axillas and groins, and the hands and feet had become soggy, pulpy masses

For twelve days, 80 mg of CORTONE were given daily, and for the next five days 100 mg per day. The oral lesions improved within twenty-four hours The patient's appetite became ravenous. On the seventh day he was walking, and on the seventeenth day was practically free from lesions In the succeeding ten weeks up to the time of reporting, 50 to 100 mg of CORTONE were injected daily On the lower dosage some erythema and pruritus recurred, but the latest reported dosage was 100 mg. a day, and the patient's condition was excellent. The skin was entirely clear except for hyperkeratosis of the palms and soles and subsiding paronychia, probably due to an arsenical and to moniliasis, respectively. The patient gained 35 pounds and returned to work.

In *scleroderma*, Kierland[18] has reported that the speed and degree of clinical improvement achieved with

On the fifth day of treatment with CORTONE definite improvement was evident: Skin on the fingers was soft and pliable, with wrinkling on the dorsum; the fist could be clenched with little restriction. Immersion of a hand in ice water for one minute no longer produced blanching of the other three extremities and blanching was less marked than formerly on the immersed hand. However, the sedimentation rate remained elevated, values of 62 and 60 mm. per hour being obtained two weeks after inception of therapy; total serum protein was 8.8 Gm., with serum albumin of 4.2 Gm. and serum globulin of 4.6 Gm. per 100 cc. Raynaud's phenomenon returned to pretreatment stage after two weeks on a dosage of 100 mg. daily by mouth.

The skin remained soft and supple, and increased mobility of the fingers was retained. The sedimentation rate fell to 21 mm. per hour after 100 mg. of CORTONE daily for one month. Improvement was maintained after a second month of treatment with 100 mg. daily. This dosage was required to maintain remission.

Dosage in Skin Conditions

(*See also* GENERAL CONSIDERATIONS, page 33.)

The dosage recommended in the treatment of skin conditions is similar to that used in rheumatoid arthritis (*see* page 34). In scleroderma, the dosage has varied widely, and some cases have required considerably more than the dosage used in rheumatoid arthritis to produce a favorable response. In pemphigus also, it generally is necessary to give higher dosage in order to prevent relapses, although small daily maintenance doses sometimes have produced adequate control.

Optimum methods and formulations for topical dermatologic application have not yet been established, nor has the effectiveness of topical therapy as compared with systemic administration been fully determined.

hours on the first day; 100 mg. every twelve hours on the second day, then 50 mg. every twelve hours for the next *twenty-six days. The patient was discharged from the hospital on a maintenance dosage of 75 mg., given daily for five days each week.*

Frank and Levitt recently reported that a patient with scleroderma and Raynaud's disease improved while being treated with CORTONE:

Case E [12]

SCLERODERMA AND RAYNAUD'S DISEASE

Female, age 20, first noted symptoms four years before ad- [illegible]

not be clenched to form a fist, and immersion of one hand in cold water for a minute caused marked blanching of fingers [illegible] Skin [illegible] open [illegible] sedi- [illegible] and globulin of [illegible] with 10 G [illegible] he dorsum of [illegible] o- derma. Rete [illegible] ge bundles of dense, sparsely cellular collagenous tissue were in [illegible]

corticotropin. Dosage of CORTONE was 300 mg. on the first day, 200 mg. on the second and third days, and 100 mg daily thereafter.

[21] Newman, B A., and Feldman, F. F.: *Calif. Med.* 75: 324–331, November 1951.
[22] Personal Communication.
[23] Silverman, M.: *A.M.A. Arch. Dermat & Syph.* 64: 524, October 1951 (in Soc. Proc). [Dermatomyositis]
[24] Sulzberger, M B., Witten, V. H., and the Skin and Cancer Unit, University Hospital and New York University Post Graduate Medical School. Personal Communication.
[25] Sulzberger, M B., Witten, V H , and Yaffe, S. N.: *A.M.A. Arch Dermat & Syph.* 64: 573–579, November 1951.
[26] Taubenhaus, M., and Lev, M *A.M.A Arch Int Med* 87: 583–593, April 1951 [Scleroderma]

ALLERGIC CONDITIONS

Therapy with CORTONE exerts a definite and, at times, spectacular ameliorative effect in a number of allergic disorders, including bronchial asthma, hay fever, allergic dermatitis, atopic dermatitis, exfoliative dermatitis, drug sensitivity, angioneurotic edema, serum sickness, transfusion reaction, and various allergic conditions of the eyes CORTONE is a valuable supplement to conventional allergic management. The improved state may consist of complete remission, or relief lasting several weeks, depending in part on the causative allergens In order to forestall relapse, the cause of the allergy should be found and eradicated whenever possible.

For additional information, *see*

Bronchial asthma . . . . . page 51
Hay fever . . . . . page 55
Skin conditions . . . . . page 68
Eye diseases . . . . . page 56
Serum sickness . . . . . page 8
Transfusion reactions . . . . . page 102

SELECTED REFERENCES

[1] Baer, R. L., and Leider, M.: *Ann. Allergy* 9: 399–416, May–June 1951.

[2] Callaway, J. L.: *Southern M. J.* 45: 63–65, January 1952

[3] Cannon, A. B., *et al.*: *J.A.M.A.* 145: 201–206, Jan. 27, 1951.

[4] Carey, R. A., Harvey, A. M , Howard, J. E., and Wagley, P. F.: *Bull. Johns Hopkins Hosp.* 87: 354–386, November 1950. [Drug reaction]

[5] Corson, E. F., and Rynes, S. E.: *A.M.A. Arch. Dermat. & Syph* 65: 112, January 1952 (in Soc Proc). [Dermatomyositis]

[6] Dorph, M. H , and Katzenstein, L.: *Delaware State M J.* 24: 50–51, February 1952.

[7] Downing, J. G.: *New Eng. J. Med.* 246: 56–65, Jan. 10, 1952.

[8] Downing, J. G.: *New Eng. J. Med.* 246: 94–101, Jan. 17, 1952.

[9] Ehrich, W. E.: *Am. Heart J.* 43: 121–156, January 1952.

[10] [illegible]

[11] [illegible]

[12] Frank, L., and Levitt, L. M.: *New York S.J.M.* 52: 353–354, Feb. 1, 1952. [Scleroderma]

[13] Franks, A., and The Skin and Cancer Unit, University Hospital and New York University Post Graduate Medical School: Personal Communication.

[14] Frazier, C N , Lever, W. F., and Keuper, C. S.: *Am J. M. Sc.* 222: 308–312, September 1951

[15] Goldman, L · Personal Communication.

[16] Hensler, N M , Wurl, O. A., and Gillespie, J O.: *U.S. Armed Forces Med. J.* 3: 199–206, February 1952.

faces, on the face, and over a recently acquired traumatic scar. Attacks of giant urticaria which had recurred for many years had become more frequent and prolonged.

During the ensuing five years, the patient had received desoxycorticosterone acetate by intramuscular injection as well as by monthly subcutaneous pellet implantations, along with supplementary sodium chloride In addition, aqueous and lipoadrenal cortex extract were given daily during rather frequent periods of intercurrent infection and minor surgery While under treatment, asthenia was decreased somewhat. The patient gained 10 pounds, attributed chiefly to increased water retention following fresh implants of desoxycorticosterone acetate

Response to CORTONE—After five years of this treatment, an [illegible]

reversed. The following year, 25 mg of CORTONE were injected daily, whereupon the patient regained the feeling of well-being and warmth, became very active, and developed a voracious appetite, with weight gain

[illegible]

patient continued to do well on this regimen, together with implantation of two 125-mg pellets of desoxycorticosterone acetate every ten months

During brief periods of infection, such as cystitis or occasional gastroenteritis, the dosage is increased to 25 mg. of CORTONE every six hours by mouth, or an injection of 100 mg once a day This precautionary measure, together with administration of suitable antibiotics, has prevented the debilitating episodes characterizing the course of the disease before CORTONE was administered

The patient has regained the weight lost during her illness and the brown pigmentation has lightened. There is a striking return of mental alertness and of normal interest in social activities.

ADDISON'S DISEASE

The Clinical Response

CORTONE is highly effective in controlling manifestations of Addison's disease. The following response to treatment has been noted. Marked improvement in morale and mental outlook; increase in muscle strength; increase in appetite and striking gains in weight, abolishment of spontaneous hypoglycemic attacks; maintenance of fasting blood sugar level, normalization of insulin tolerance and insulin-glucose tolerance tests; increase in plasma proteins, restoration of normal electroencephalogram; decrease in skin pigmentation; restoration of normal red blood cell count, hemoglobin and hematocrit values; resistance to infection enhanced, virtual abolition of adrenal crises. CORTONE does not necessarily represent complete maintenance therapy, in most patients added salt or desoxycorticosterone is necessary.

The following typical case history[4] illustrates how a patient with Addison's disease showed far better response to therapy with CORTONE than to measures employed in the preceding five years:

Prior to Therapy with CORTONE—A diagnosis of Addison's disease was confirmed in a 53-year-old woman in 1943 on the basis of characteristic history, physical and laboratory findings, including low serum sodium, elevated serum potassium concentration, and greatly reduced ketosteroid excretion. The heart was 17 per cent below normal average size, and the blood pres- [illegible]

mission, the woman complained of progressive weakness, listlessness, and cold, recurrent attacks of nausea and vomiting, and increasing brown pigmentation—especially over joint sur-

DISSEMINATED LUPUS ERYTHEMATOSUS

The Clinical Response

When used early in the course of disseminated lupus erythematosus, CORTONE produces a beneficial effect in most cases. CORTONE is the first agent to exert some measure of control over the progressive decline which usually occurs in patients with this disease.

The use of CORTONE is particularly beneficial where *irreversible tissue damage has not taken place. Prompt and* striking remissions are promoted in some cases, lasting from several days to weeks or months Although the basic disease process does not appear to be altered, therapy with CORTONE frequently is lifesaving. With adequate dosage the following evidences of improvement are observed: (*1*) Suppression of arthralgia, fever, skin lesions, and serositis, and improvement in the sense of well-being, together with increased appetite and gain in weight, (*2*) Ability to withstand stress and crises such as major operations and infections, including pneumonia, abscesses, and septicemia, which are ordinarily disastrous in this disease; (*3*) A degree of remission may take place. (Although remission may occur in the natural course of the disease, it is exceptional in the acute phases) These effects generally last from a few days to a few weeks, and even longer in some patients Symptoms may return within a few days to several weeks after the use of the hormone is discontinued.

The favorable effects produced by CORTONE cannot be expected in late cases with advanced renal involvement, azotemia, hypoproteinemia, retinal hemorrhages, and cachexia Because of the frequency with which the heart and kidneys are involved in this disease, patients should be closely watched for evidence of aggravation of sodium

Dosage in Addison's Disease

(*See also* GENERAL CONSIDERATIONS, page 33.)

CORTONE is given in doses of 10 or 12.5 to 25 mg. daily, parenterally or orally, with 4 to 6 Gm. of supplementary sodium chloride or doses of 1 to 3 mg of desoxycorticosterone acetate. This regimen usually will maintain the blood electrolytes at normal values and effect pronounced general improvement. Objective signs of this include return of the abnormal electroencephalogram toward normal and the re-establishment, in some cases, of a normal diuretic response to ingested water (Robinson-Power-Kepler test).

In addisonian crisis, and in instances of intercurrent infection or surgical procedures in patients with Addison's disease, at least 100 to 300 mg. of CORTONE should be administered daily until the unusual stress no longer exists and normal food intake has been restored.

Some clinicians recommend supplementing CORTONE with large injections of adrenal cortical extract in times of acute stress, to obtain a more rapid effect, also if vascular collapse limits absorption of CORTONE administered intramuscularly, and oral dosage is not feasible.

SELECTED REFERENCES

1 Bonner, C D.: *J.A.M.A.* 148: 634–637, Feb. 23, 1952.
2 Forsham, P. H, *et al.* *J. Clin. Endocrinol.* 9: 660, July, 1949 (in Soc. Proc)
3 Levy, M. S.: *J.A.M.A.* 149: 411–415, May 31, 1952.
4 Personal Communication.
5 Salassa, R. N.· *Proc. Staff Meet*, *Mayo Clin* 25: 497–498, Aug. 16, 1950.
6 Schwartz, H, Derrick, W. S, and Papper, E. M.· *Surg., Gynec. & Obst.* 94: 455–463. April 1952.

was instituted in the hope that the progress of the disease could be stayed or arrested It was found that the hormone is of greatest value in tiding patients over the critical period of acute episodes; in such cases, it may be lifesaving.

The well-known symptomatology of lupus erythematosus disseminatus was present in varying degrees in all nine patients (dermatologic manifestations, arthritis, febrile course, anemia, leukopenia, and renal involvement). The L E. cells of Hargraves were demonstrated in the sternal marrow of seven of the nine patients. The usual laboratory studies were repeated, generally every week Bone marrow aspirations were done at the end of [illegible]

given. The interrupted schedule seemed somewhat more satis- [illegible]

wards than before However, CORTONE appeared to be very valuable in tiding another patient over an acute episode with pericarditis and pleuritis, and she has remained as well since cessation of therapy as before

In only one patient, with a history of mental disease, did therapy have to be discontinued because of a psychosis and various other complications. Ascites developed in another patient Possible complications should be watched for so that dosage can be reduced or therapy stopped, and proper measures for control instituted Limitation of salt intake will lessen the likelihood of edema and ascites, and 3 Gm per day of potassium chloride might be advisable, although these authors merely determined potassium and sodium blood levels frequently, usually once a week.

In five of the nine patients who had received *para-amino*-benzoic acid previously with favorable results, the response to CORTONE was more rapid.

and water retention and congestive heart failure. It is *advisable to limit the intake of sodium salts and to administer* potassium chloride in order to offset the development of edema and hypopotassemia. It also should be borne in mind that patients with lupus erythematosus are commonly subject to a variety of serious complications, including convulsive seizures, incidents of sudden death are not at all rare, regardless of the form of treatment.

To maintain improvement, prolonged or even permanent maintenance dosage of CORTONE is usually required, along with careful observations for hormonal side effects.[12] (For adjunctive measures, *see* page 17.) Very large doses of CORTONE were used to control acute lupus crisis in the following case:

Crisis developed in a 13-year-old girl with systemic lupus erythematosus, although maintenance dosage was increased gradually to 250 mg. daily On the second day of the crisis, 350 mg. of CORTONE were given orally. Dosage was increased on the third day to 900 mg. intramuscularly, 1,050 mg intramuscularly on the fourth day, and 2,300 mg. intramuscularly on the fifth day (injected every hour). On the sixth day, 1,400 mg were given orally, and 900 mg. orally on the seventh day. The acute lupus crisis was controlled and partial remission was obtained by these high doses, which were reduced after the administration of nitrogen mustard No undue hormonal effects due to CORTONE were reported, but it should be noted that massive dosage was employed for a few days only during the acute lupus crisis.[6, 7]

Therapy with CORTONE has produced beneficial effects on the epileptiform seizures that may develop in conjunction with disseminated lupus erythematosus. Epilepsy is an important and frequent central nervous system manifestation in this disease.[11]

Johnson and Meyer[10] report results of therapy with CORTONE in nine women suffering from acute or subacute forms of disseminated lupus erythematosus. This therapy

Dosage in Disseminated Lupus Erythematosus

(*See also* GENERAL CONSIDERATIONS, page 33.)

After two or more days of intensive therapy (200–300 mg.), 100 mg of CORTONE daily are required to control symptoms in most patients. In all cases, however, the dosage depends on the response of the patient to the drug. Acute exacerbations of the disease require high doses. These may be gradually reduced until a minimum maintenance level is reached below which arthritis, fever, and other evidences of clinical activity are observed to occur. Relapse usually follows decrease in dosage or discontinuance of treatment.

SELECTED REFERENCES

[1] Baehr, G , and Soffer, L. J *Bull New York Acad. Med.* 26: 229–234, April 1950

[2] Brunsting, L A , Slocumb, C. H , and Didcoct, J W.: *A.M.A Arch. Dermat. & Syph.* 63: 29–52, January 1951.

[3] Downing, J. G.: *New Eng J Med.* 246: 56–65, Jan. 10, 1952

[4] Downing, J. G.: *New Eng. J Med* 246. 94–101, Jan 17, 1952.

[5] Dubois, E L , *et al* · *J A M A* 149: 995–1002, July 12, 1952

[6] Haserick, J R., Corcoran, A C., and Dustan, H. P.: *Cleveland Clinic Quart.* 18: 117–118, April 1951

[7] Haserick, J. R., Corcoran, A. C., and Dustan, H. P.: *J.A M.A* 146: 643–645, June 16, 1951.

[8] Hench, P S *Ann Int Med.* 36: 1–38, January 1952.

[9] Irc [illegible]

[10] Jo [illegible]

[11] Russell, P W., Haserick, J R , and Zucker, E M.: *A.M.A. Arch. Int Med* 88: 78–92, July 1951.

[12] Soffer, L. J., Levitt, M. F , and Baehr, G : *Arch. Int. Med.* 86: 558–573, October 1950

[13] Soffer, L. J., and Bader, R.: *J.A.M.A.* 149: 1002–1008, July 12, 1952.

Two individual case histories included in the above series are presented to show the favorable results that may be obtained with CORTONE:

A 20-year-old girl had joint symptoms, urticarial lesions, and L.E. cells in the bone marrow. Therapy with para-aminobenzoic acid for over a year had brought good results. CORTONE, given for fifty days, resulted in additional subjective and objective improvement for eight months, and was extremely useful during a period of several months of acute illness.

Therapy with CORTONE was begun because the patient developed pleuritis and pericarditis Dosage was 50 mg. intramuscularly four times a day for ten days, then 50 mg. twice daily for forty days.

After the first week of treatment the electrocardiographic findings indicated improvement in the pericarditis. By the second week the patient felt very well and had a good appetite. Roentgenogram of the chest showed that the fluid in the left pleural cavity had disappeared and that the heart had returned to normal size. Roundness of the face and hirsutism of the upper lip were seen during the third week of treatment.

Examination about a year after discontinuing treatment with CORTONE revealed continued subjective and objective improvement. A few L E. cells still were present in the bone marrow. The patient is continuing college work on a reduced schedule

A 27-year-old woman had a history of frequent sore throat (streptococcic infection) and a severe sunburn at the onset, which many observers have noted as precipitating factors in this disease Loss of joint symptoms, decrease in skin lesions, [illegible]

she felt jittery and had some difficulty with her hearing and sense of taste During the second week, after the first course, she had an excellent appetite and felt better than she had in years. Improvement after the second course was less marked Four months after completion of therapy, there was continued subjective and objective improvement

direction The usual shoulder exercises were prescribed for moderate muscular weakness resulting from long immobilization. The patient returned to work, and follow-up examinations during the succeeding three months have shown no evidence of recurrence.

Dosage in Bursitis

(*See also* GENERAL CONSIDERATIONS, page 33.)

In many cases of bursitis, CORTONE has been administered as follows 100 mg. every eight hours, first day; every twelve hours, second day; gradual reduction of dosage over the succeeding four to eight days.

SELECTED REFERENCES

[1] Friedman, M · *Maryland State M J* 1: 186–188, April 1952.
[2] Personal Communication

PULMONARY GRANULOMATOSES

Effective results with CORTONE are reported in berylliosis, sarcoidosis, and certain cases of unknown etiology.

Berylliosis

The pulmonary granulomatosis encountered in beryllium poisoning has shown the best response to CORTONE. Twenty or more cases treated with CORTONE, corticotropin, or combinations, have been reported by investigators. With high initial dosage, more than half the cases show definite improvement which can be maintained by continued dosage—and reduced when possible Dyspnea is promptly relieved, with a sharp diminution in hyperpnea. The lung volume may increase somewhat, but the main effect is a marked improvement in diffusion, as represented by better oxygenation of the blood and a lesser oxygen gradient from the alveolus to the capillary. Pulmonary hypertension is sometimes reduced. Many patients have

BURSITIS

The Clinical Response

In the treatment of bursitis, CORTONE has produced highly effective results. Within a few days after the beginning of therapy, patients may be expected to regain normal range of motion and be free from pain and tenderness—as illustrated in the following case report:[2]

A 39-year-old male was admitted to the outpatient department in July 1951, complaining of severe pain and limitation of motion of the left shoulder. Three weeks previously the patient [illegible]

the area of the infraspinatus tendon, and led to the diagnosis of acute calcific tendonitis and bursitis. X-ray treatments failed to improve the condition.

Four days later, the patient entered the clinic for further observation and treatment. At this time, the shoulder was warm, exquisitely tender to palpation, and there was marked limitation of all motion. Passive movement in any plane elicited severe pain Otherwise, physical examination was negative, and there was no evidence of residual tonsillitis.

Because heat and X-ray treatment proved ineffective, ther- [illegible]

completely absent. There was no limitation of motion in any

come progressively worse The patient had to be led into the hospital and she could see only hand movements. The cornea of the right eye was almost completely opaque in the inferior temporal zone and in the pupillary area. Dense opacities covered the lower half of the cornea of the left eye The vitreous was cloudy in both eyes. Deep corneal infiltrates and bilateral vascularization were revealed by slit-lamp examination. Unpigmented keratic precipitates studded the posterior surfaces of the cornea.

X-ray revealed enlargement of lymph nodes in both hilar and right paratracheal areas, noted six months before admission. Two six-month-old Nickerson-Kveim reaction papules revealed the typical sarcoid-like structure of a positive reaction on microscopic examination

CORTONE was administered intramuscularly for fifteen weeks. Daily dose usually was 150 mg, totaling 13 7 Gm. Visual acuity improved greatly After one day, the patient could count fingers at a distance of two feet, by the twelfth day she could walk about the ward alone, on the sixteenth day she could read large type in a newspaper, at the end of four weeks the vision in each eye was 20/100.

This recovery was paralleled by objective improvement In the second week the injection of the scleral and ciliary vessels disappeared, in the third week the vascularization of the cornea receded and the keratic precipitates diminished.

The corneal opacities dwindled in the fourth week, and in the ninth the vitreous cleared The patient's improvement was maintained

On the third day, the papules of the Nickerson-Kveim skin test had begun to flatten and pale. Biopsy on the twenty-ninth day showed regression of the granulomas and replacement by a fibrous scar

The patient left the hospital with 76 per cent of normal binocular vision Mild exacerbation of uveitis developing three weeks after CORTONE was discontinued, was controlled easily

reported improved appetite which has resulted in weight gain. Outlook on life has become much more cheerful. After cessation of therapy, tremendous variation has been observed. Some patients, after several months of treatment, can continue without further administration of the hormone and without showing regression. Most cases regress—some quickly, others gradually.

Sarcoidosis

CORTONE frequently causes regression of pulmonary, lymphoid, ocular and skin manifestations in this disease. Although the periods of remission may be variable, the results often are strikingly beneficial. CORTONE appears to be of value in reducing the activity of lesions and minimizing damage to vital organs during exacerbations. Further study is needed to determine whether the natural course of the disease is affected and whether the early use of CORTONE, before scar tissue is laid down, can prevent the crippling sequelae of sarcoidosis.

Favorable responses to 100 mg daily of CORTONE were obtained in three of eight fairly advanced cases of sarcoidosis, manifested by considerable lessening of dyspnea, reduction of hyperpnea, little change in lung volume, and a significant improvement in blood oxygenation

Another twelve patients with pulmonary sarcoidosis all responded to CORTONE extremely well, with easily measurable physiologic changes. In several, radiologic changes reappeared fairly rapidly at the end of treatment, but the patients have remained much less incapacitated with regard to their pulmonary function.

The following case report shows some of the more favorable effects which may be obtained with CORTONE:[4]

A woman, age 30, had enlargement of the mediastinal lymph nodes and severe bilateral ocular sarcoidosis. Despite standard treatment, the ocular lesions, present for eight months, had be-

WATERHOUSE-FRIDERICHSEN SYNDROME

Clinicians report good response to therapy with CORTONE in this syndrome. Successful results were obtained in an 11-year-old boy with three intramuscular injections of 37.5 mg. of CORTONE given at six-hour intervals. A 28-year-old woman responded to five 100-mg. doses given every six hours. The hormone was used along with conventional therapy.

Patients with Waterhouse-Friderichsen syndrome require immediate and massive substitution therapy to protect the circulatory system, blood sugar levels, and resistance to bacterial and viral infection. In addition to administration of CORTONE, there must be support of the plasma volume and blood pressure, prevention of hypoglycemia, and appropriate antibacterial therapy.

(*See also* GENERAL CONSIDERATIONS, page 33.)

SELECTED REFERENCES

[1] Fowler, J. T., Jr. *California Med* 75: 369, November 1951.
[2] Harvey, H. P. B. *M. J. Australia* 1: 222–224, Feb. 16, 1952.
[3] Nelson, J., and Goldstein, N. *J.A.M.A.* 146: 1193–1197, July 28, 1951.
[4] Newman, L. R.: *J.A.M.A.* 146: 1229–1230, July 28, 1951.
[5] Papper, E. M., and Cahill, G. F.: *J.A.M.A.* 148: 174–179, Jan. 19, 1952.

ADRENOGENITAL SYNDROME

The adrenogenital syndrome with its progressive virilization has been reported to be controlled by the administration of CORTONE. The overactivity of the adrenal cortex

sodium or fluid retention while the patient was on a low sodium [illegible]

33 and 88 per cubic millimeter while the drug was administered The patient had a hearty appetite and gained 26 pounds, mostly during the last six weeks of therapy.

No relapse has occurred in the eleven months' follow-up period since CORTONE was discontinued The patient was able to resume her usual activities.

Dosage in Pulmonary Granulomatoses

Dosage in berylliosis and sarcoidosis is similar to the conservative dosage schedule outlined under Rheumatoid Arthritis, page 34. (*See also* GENERAL CONSIDERATIONS page 33)

SELECTED REFERENCES

[1] Kline, E M., Inkley, S R., and Pritchard, W. H.: *A.M.A. Arch. Indust. Hyg & Occup Med* 3: 549–564, June 1951.

[2] Longcope, W. T, and Freiman, D. G : *Medicine* 31: 1–132, February 1952.

[3] Lovelock, F. J., and Stone, D J *J.A M.A* 147: 930–932, Nov 3, 1951.

[4] Siltzbach, L. E., *et al: J.A.M.A* 147: 927–929, Nov. 3, 1951.

[5] Siltzbach, L. E.: *Am. J Med.* 12: 139–160, February 1952.

[6] Sones, M., Israel, H L, Dratman, M B, and Frank, J H. *New England J. Med* 244: 209–213, Feb 8, 1951

[7] Van Ordstrand, H S. *Ann Int. Med.* 35: 1203–1217, December 1951

[8] Wright, G W.. *A.M.A. Arch. Indust. Hyg. & Occup. Med* 3: 617–621, June 1951.

inject 75 mg. every third day, or 100 mg every fourth day, instead of giving 25 mg daily.) Some investigators have reported that when CORTONE is given *orally*, two or three times these amounts are required, *i.e*, 12 to 75 mg daily, given in two to three divided doses. Patients with defective electrolyte regulation (dehydration and other addisonian-like symptoms), as well as androgenic manifestations should be treated with high sodium chloride intake and/or desoxycorticosterone in addition to CORTONE.

(*See also* GENERAL CONSIDERATIONS, page 33.)

SELECTED REFERENCES

Adrenogenital Syndrome and Pseudohermaphroditism

[1] Hinman, F, Jr: *J Clin Endocrinol* 11. 477–486, May 1951.

[2] Wilkins, L, *et al* *J Clin Endocrinol & Metab.* 12: 277–295, March 1952

[3] Wolman, B · *Brit M J* 1: 244, Feb 3, 1951 (in Soc Proc).

ADRENALECTOMY

Administration of CORTONE has proved helpful in patients undergoing adrenalectomy for hypertension, Cushing's syndrome, or neoplastic diseases. In cases of adrenalectomy performed for *severe hypertension*, 100 to 200 mg of CORTONE have been given on the day of the *second* operation; first postoperative day 100 mg and 2 5 mg of desoxycorticosterone acetate, second and third postoperative days 37 5 mg, thereafter, daily doses of 12 5 to 25 mg with supplementary sodium chloride and/or 1 to 3 mg. of desoxycorticosterone acetate.

In *Cushing's syndrome*, 200 mg of CORTONE are given preoperatively, postoperative dosage is 200 mg daily, tapering off within three to four weeks.

Results of therapy with CORTONE also have been reported on a series of *cancer* patients, selected for simul-

is suppressed when the drug is given in small amounts that cause no abnormal metabolic or hormonal effects. Studies have shown excellent results in patients varying in age from eleven weeks to eighteen and one-half years. In young female *pseudohermaphrodites* (over nine years of age), there has been a decrease in virilization and hirsutism, a rapid development of secondary sex characteristics with breast development, estrogenic changes of vaginal smears, and the establishment of regular menstrual cycles.

In each case, it is important to determine the minimum dose of CORTONE capable of bringing about adequate suppression of adrenal hyperactivity. This minimum dose is determined by measuring the urinary excretion of 17-ketosteroids.

Children under six years of age normally excrete less than 1 mg. of 17-ketosteroids in twenty-four hours. In normal adult women, during the reproductive period, the 17-ketosteroid excretion usually ranges from 5 to 15 mg. in twenty-four hours. The menstrual cycle does not cause cyclic fluctuations in the 17-ketosteroid excretion In adult men, the range is from 7 to 20 mg in twenty-four hours, although values up to 27 mg. have been regarded as normal. The higher values in men are attributed to the fact that the testes contribute to the total 17-ketosteroid output, while in women the ovaries do not (excluding estrone). However, possible differences in adrenal cortical function *in the two sexes must be kept in mind*

To obtain rapid suppression of the adrenal, it is advisable to give infants or younger children intramuscular injections of 25 mg. of CORTONE daily during the first week, children over eight years of age should be given 50 mg. daily. After this, maintenance doses of CORTONE should be begun intramuscularly, ranging from 6 mg per day in infants to 25 mg. per day in older children and adults. (In some instances, it has been found practical to

shortly after operation, two were unaffected, and four were apparently greatly improved. No beneficial effect was obtained in the four patients with other types of cancer.

SELECTED REFERENCES

[1] Harrison, J. H., Thorn, G. W., and Criscitiello, M. G.: *J. Urology* 67: 405–413, April 1952.

[2] Huggins, C., and Bergenstall, D. M.: *J.A.M.A.* 147: 101–106, Sept. 8, 1951.

[3] Papper, E. M., and Cahill, G. F.: *J.A.M.A.* 148: 174–179, Jan 19, 1952.

[4] Thorn, C. W., Frawley, T. F., Forsham, P. H., and Wilson, D. L.: *J. Clin. Endocrinol.* 11: 774–775, July 1951 (in Soc. Proc.)

MALIGNANT DISEASES

In patients with cancer, particularly in the terminal stages, treatment with CORTONE produces a sense of well-being *that is beneficial to the patient and enables him to endure* his illness in a better frame of mind. Concomitantly there frequently is reduction of pain and increased appetite.

Cancer of the prostate and breast respond to administration of CORTONE *in much the same* way that they would respond to adrenalectomy: presumably less sex hormone is elaborated by the adrenal cortex and thus aggravation of the carcinoma is curtailed. At the same time, CORTONE exerts a beneficial effect on the patient's general condition.

In the *lymphomas,* CORTONE has a direct, though temporary, inhibitory effect on the neoplastic process, as well as a palliative action, which is of marked benefit to many patients.

Young adult patients with *acute leukemia* occasionally benefit substantially, although temporarily, when therapy with CORTONE is used. Fifty per cent of children improve for periods up to three months on 200 mg. daily. Even in

taneous bilateral adrenalectomy. Patients with prostatic cancer fulfilled the following criteria: all patients had far-advanced metastatic tumors which could be demonstrated objectively, and all had been treated by antiandrogenic measures without control of the tumor. Among the thirty three patients in this series, twenty-nine consecutive cases were treated without a fatality and with very little morbidity. In all, only two deaths occurred.

The regimen employed was as follows: One day prior to operation, 200 mg. of CORTONE plus 5 mg. of desoxycorticosterone acetate were administered. On the day of operation, [illegible] acetate [illegible]

acetate to prevent adrenal insufficiency during and after adrenalectomy, the patient was placed on a hormone-substitution program within one week. In most cases, this has proved to be a satisfactory maintenance regimen. The criterion for adequate substitution is the prevention of any signs or symptoms of adrenal insufficiency Determination of serum electrolytes and maintenance of an adequate blood pressure without orthostatic hypotension are the best indicators.

[illegible] 25 [illegible] me [illegible] NE [illegible] ial [illegible] not require maintenance doses of desoxycorticosterone acetate.

The majority of the patients thus far maintained five to ten months postoperatively had *prostatic cancers*, or *mammary cancers* The remaining cases include squamous carcinoma, chorioepithelioma, melanosarcoma, and cancer of the lung. The two fatalities consisted of one patient with prostatic, one with mammary, cancer.

Four patients in the prostatic series displayed presumptive or certain evidence of improvement namely decrease in the size of the lesion, decrease of phosphatase, increase in hemoglobin

Of the seven patients with mammary cancers, one died

SELECTED REFERENCES

[1] Bell, R. E, and Thomson, R. K., *Canad. M.A.J.* **64:** 43–47, January 1951 [Leukemia.]
[2] Block, M, and Jacobson, L O *Cancer Research* **12:** 250, April 1952 (in Soc Proc) [Lymphomas]
[3] Ehel, L. P., and Pearson, O. H.: *N. Y. State J. Med.* **51:** 1839–1843, Aug 1, 1951.
[4] Fishman, H. C: *Urol. & Cutan Rev.* **55:** 319, May 1951.
[5] Hines, D. C.: *Pennsylvania M. J* **54:** 1045–1051, November 1951 [Myeloma]
[6] Huggins, C, and Bergenstal, D M.: *Cancer Research* **12:** 134–141, February, 1952
[7] Limarzi, L. R., Paul, J. T, and Best, W. R *J. Lab. & Clin Med* **38:** 922–923, December 1951 (in Soc. Proc.). [Myeloma]
[8] Marchal, G, Duhamel, G, Camus, T, and Camus, J P · *J.A.M.A.* **148:** 1143, March 29, 1952 (in Foreign Letters, Paris). [Myeloma]
[9] Nathanson, I. T, and Kelley, R. M.: *New Eng. J. Med.* **246:** 135–145, Jan 24, 1952.
[10] Nathanson, I. T, and Kelley, R. M: *New Eng J. Med.* **246:** 180–189, Jan 31, 1952
[11] Pearson, O H, and Ehel, L P *J.A.M.A* **144:** 1349–1353, Dec 16, 1950 [Lymphomas, Leukemia.]
[12] Riser, W. H., Jr.: *J.M.A Alabama* **20:** 317–319, March 1951
[13] Schulman, I, Lanman, J T, Laxdal, O. E, and Holt, L. E, Jr *J Pediatrics* **8:** 34–52, July 1951. [Leukemia]
[14] Smith, R H *U.S Armed Forces M. J* **2:** 1787–1794, December 1951. [Leukemia]
[15] Stickney, J M, Heck, F. J, and Watkins, C. H · *Proc Staff Meetings, Mayo Clin* **25:** 488–489, Aug 16, 1950. [Leukemia, Lymphoblastoma]
[16] Taylor, S G III, Ayer, J P., and Morris, R. S, Jr: *J A M.A* **144:** 1058–1064, Nov. 25, 1950.

cases where there is an initial response, refractoriness to the substance develops during repeated courses of CORTONE. Patients with *chronic lymphatic leukemia* respond regularly to this therapy. Remissions, though not complete, are characterized by shrinkage of lymphoid masses, a rise in or better maintenance of hemoglobin levels, and increase in appetite and general well-being. Development of resistance to therapy is less of a problem than in acute leukemia and some patients have benefited from several courses of therapy with CORTONE. *Chronic myeloid leukemia* has shown no response to therapy with CORTONE in several cases treated.

In *lymphosarcoma* and *Hodgkin's disease* CORTONE produces dramatic and prompt recession of enlarged lymph glands, but after cessation of therapy (and eventually on continued treatment) nodes return to their former size.

CORTONE may give relief of pain and sometimes produce temporary regression of lesions in patients with *multiple myeloma* Pain due to bone lesions often may be 90–100 per cent relieved by therapy with CORTONE. When used alone or as an adjunct to X-ray, CORTONE in addition to its direct effects produces a certain degree of euphoria. Treatment can be stopped after a week or so, and the pain in some cases has not recurred for four to six weeks.

Dosage in Malignant Diseases

(*See also* GENERAL CONSIDERATIONS, page 33)

In general, the dosage employed has been similar to that outlined for rheumatoid arthritis, page 34

In *acute leukemia*, as mentioned above, about 50 per cent of children improved for a period up to three months on 200 mg of CORTONE daily. Second responses are hard to obtain and third ones rarely, if ever, occur.

In *lymphoblastoma* no undesirable physiologic effects have been observed from a daily dosage of 300 mg. orally.

[6] Adlersberg, D , Colcher, H , and Drachman, S. R.: *Gastroenterology* 19: 674–697, December 1951.
[7] Badenoch, J.: *Brit. M J* 1: 356–357, Feb. 16, 1952.
[8] Pollack, A. A , and Pollack, H.: *N. Y. State J. Med.* 51: 2264, Oct 1, 1951.
[9] Taylor, A B , Comfort, M. W., Wollaeger, E E , and Power, M. H . *J. Clin. Invest* 30. 678, June 1951 (in Soc. Proc)
[10] Freeman, J *J.A.M.A* 146: 396, May 26, 1951 (Correspondence).
[11] Ley, A. B , and Gardner, F. H . *J. Clin Invest.* 30: 656, June 1951 (in Soc. Proc).
[12] Kugelmass, I. N., *N. Y. State J. Med* 51: 2504–2506, Nov. 1, 1951.
[13] Stefanini, M , *et al Blood* 7: 53–76, January 1952.
[14] Cohen, S . *Ann Western Med. & Surg* 4: 288–293, June 1950
[15] Papper, E M , and Cahill, G. F.: *J.A.M.A* 148: 174–179, Jan 19, 1952.
[16] Priestley, J. T , Sprague, R. G., Walters, W , and Salassa, R M *Ann Surg* 134: 464–475, September 1951.
[17] Doerner, A. A , *et al J.A.M.A* 147: 1099–1101, Nov 17, 1951.
[18] Holmes, M E . *N. Y State J. Med* 52: 175–179, Jan 15, 1952.

OTHER CONDITIONS

Effective results with CORTONE have been reported in diversified conditions such as *early periarteritis nodosa*,[1-4] *Hunner's ulcer*,[5] and *sprue*.[6-9] The dosage employed in these conditions has been similar to the conservative dosage schedule outlined under rheumatoid arthritis, page 34. (*See also*, GENERAL CONSIDERATIONS, page 33.)

In *laryngeal edema*,[10] *acquired hemolytic anemia*,[11] and *allergic purpura*,[12] initial doses of 200 to 300 mg. have been employed, followed by 100 to 200 mg. on the second day; from the third day on, 100 mg of CORTONE are given, with gradual reduction to maintenance dosage

Idiopathic thrombocytopenic purpura.[13] Administration of CORTONE has induced remissions in patients with this disease. In one series of cases, oral doses of 75 mg. every six hours were used.

In *Cushing's syndrome*,[14-16] 200 mg. of CORTONE are given preoperatively, postoperative dosage is 200 mg, tapering off within three to four weeks. *Rh incompatibilities*[17] and *transfusion reactions*[18] have been reported to respond to CORTONE. Daily dosage used in Rh incompatibility is 100 mg during the last two months of pregnancy, in transfusion reactions, 200 to 300 mg.

SELECTED REFERENCES

1 Baggenstoss, A. H, Shick, R. M., and Polley, H. F· *Am. J. Path* 27: 537–559, July–August 1951
2 Frankel, A L, and Rothermich, N. O: *Ohio State M J* 47: 1013–1021, November 1951.
3 Shick, R M, Baggenstoss, A H, Fuller, B F, and Polley, H F. *Proc. Staff Meetings, Mayo Clin.* 25: 491–492, Aug 16, 1950.
4 Shick, R. M, Baggenstoss, A H., Fuller, B F, and Polley, H. F· *Minnesota Med.* 34: 852–853, November 1951.
5 Van Duzen, R. E, and Mustain, R.. *J Urol* 65: 1033–1040, June 1951.

Corticosteroids· The urinary concentrations of corticosteroids are initially increased by administration of CORTONE and may reach a peak of excretion of about 5 mg per twenty-four hours soon after treatment is started The amount excreted then declines gradually to a fairly constant level, ranging from 1 to 2 mg. per twenty-four hours, on continued administration of the hormone. On discontinuing CORTONE following prolonged treatment periods or after the injection of large doses, both 17-ketosteroid and corticosteroid excretion has been observed to diminish temporarily below pretreatment levels in certain patients.

LABORATORY FINDINGS FOLLOWING ADMINISTRATION OF CORTONE

Erythrocyte Sedimentation Rate: Elevated sedimentation rates are decreased, sometimes rapidly, during the administration of CORTONE, usually becoming normal within 10 to 35 days. Occasionally, however, the rate does not return to normal, but is definitely reduced. In a few instances, persistently high sedimentation rates may be lowered by temporarily increasing the daily dose of the hormone

Hemoglobin: Low hemoglobin values tend to increase when CORTONE is administered. Increases of 2.5 Gm. within several weeks have been observed

Blood Cells. Increases of as much as 1,000,000 red cells per cu. mm. of blood have been observed in anemic patients during therapy with CORTONE for two weeks or longer. A mild increase in the leukocyte count may occur in some patients.

Serum Protein: Increased serum globulin levels and low or reversed albumin-globulin ratios usually return toward normal, in most cases promptly, during treatment, but gradually revert to pretreatment levels when the hormone is discontinued.

17-Ketosteroids· The effect of CORTONE is variable, depending on the dosage, which, if high, tends to increase the 17-ketosteroid values. The effect depends also on the degree of adrenocortical depression resulting from administration of CORTONE.

renal insufficiency; latent or overt psychotic tendencies; *diabetes mellitus; known or suspected peptic ulcer;* and the presence of recent surgical sites, *e g.*, intestinal anastomoses. (The healing of skin wounds is seldom, if ever, adversely affected.)

The presence of active or questionably healed tuberculosis is an almost absolute contraindication. So, too, are other acute or chronic infections. If it becomes mandatory *to give* CORTONE *despite such contraindications*, adequate and appropriate antibiotic or other chemotherapeutic measures are essential. An X-ray of the chest should be taken in every patient who is to be treated with CORTONE for any considerable period of time, and repeated at appropriate intervals.

In osteoporosis, administration of CORTONE may further increase calcium excretion and inhibit formation of bone matrix, consequently, treatment with this hormone should be undertaken with caution in such cases and should be accompanied by measures designed to counteract further osteoporosis.

DETECTION AND PREVENTION OF UNDESIRED EFFECTS

Metabolic Effects

Simple measures may be employed to recognize undesired metabolic effects—such as salt and water retention, hyperglycemia, and transient glycosuria—that may be caused by CORTONE. The only diagnostic procedures required are *those customarily used by physicians, e.g., blood pressure* readings, blood counts, urinalyses, and weight recordings While such studies should be made every few days when higher doses are used, examinations every two to six weeks are sufficient when lower maintenance doses are employed.

Tolerance

With appropriate adjustment of dosage, satisfactory therapeutic response usually can be maintained with a minimum of undesired physiologic effects.

CORTONE is a potent substance and definite physiologic effects are to be expected from its administration. When given in prolonged high dosages and, in certain patients in recommended dosage, a number of effects other than the dominant therapeutic effect may occur. Some of these clinical and biochemical effects are desirable; they include: the antipyretic effect; the nutritional effect, with increased appetite, strength, and weight; the "psychic effect," with euphoria and increased mental energy, provided there is no nervous irritability or other undesirable changes in mood; the biochemical effect, with increase in hemoglobin and erythrocyte count, and return toward the normal ratio of serum proteins.

Other effects, however, may be undesirable. The patient receiving CORTONE should be observed closely for the possible development of undesirable effects. These effects are to be respected but not feared. They are fully *reversible* and disappear after the administration of CORTONE is discontinued. Measures for the prevention or elimination of possible undesired effects are described on page 107.

Relative Contraindications

As in the case of other powerful agents having potentially harmful effects, the physician should weigh the advantages of treatment with CORTONE against its possible deleterious effects. This consideration is particularly crucial where relative contraindications exist, such as diminished cardiac reserve or congestive heart failure; hypertension;

may be avoided by a low sodium, high potassium diet. (ECG findings frequently are the best clue to low cellular potassium levels.)

Although hypopotassemia is an uncommon complication, it may occur quite suddenly. Therefore, if electrocardiography is not available it is a wise precaution to prescribe potassium chloride, 1 Gm. daily, if the maintenance dosage of CORTONE is 100 mg. or more per day. In some instances, the prophylactic administration of testosterone also may be advisable

The use of potassium salts must be avoided or entered upon with great caution in the presence of renal impairment or cardiac decompensation.

If any changes indicating hypochloremic, hypopotassemic (metabolic) alkalosis are noted, potassium may be administered orally (1 to 4 Gm. KCl, per day, depending on body weight), or the dosage of CORTONE may have to be reduced in some cases. It should be remembered that the tissues may be low in potassium even when blood potassium levels appear adequate. Diuretics, if used, should be employed cautiously, since they may provoke a further dangerous loss of potassium

Conversely, if potassium excretion is impaired because of renal insufficiency or congestive heart failure, symptoms of hyperpotassemia may develop as a result of potassium administration. Elevation of serum potassium may produce paralysis or cardiac arrest and marked ECG abnormalities, including elevated T-waves, absent P-waves, interventricular block, and irregularities of rhythm.

Hyperglycemia Carbohydrate metabolism may be affected, with increase in blood sugar levels and decreased response to insulin. In patients with diabetes mellitus, insulin requirements are increased during administration of CORTONE, but revert to their original levels soon after its

Sodium and Water Retention: Electrolyte balance is affected in varying degrees in different patients. Retention of sodium and water early in the course of treatment often is observed, especially when high dosages of CORTONE are employed (*e.g.*, 200 mg. per day), but is usually followed by spontaneous diuresis on continued administration of the hormone or following its discontinuance. In most of these cases there is only minimal edema and a weight gain of a few pounds. In some instances, however, this may progress and result in pronounced edema, including pulmonary edema or cardiac enlargement and congestive failure, especially in patients with diminished cardiac reserve. Occasionally, such signs and symptoms may come on quite suddenly and there may be some elevation of arterial blood pressure. Sodium and water retention may be sufficient in some cases to require lowering the dosage or discontinuing administration.

Measurement of fluid intake and output, and frequent weighing and examination of the patient, provide the best indices of fluid retention. The simplest preventive of salt and fluid retention is a low sodium diet, with sodium intake *kept below 1 Gm daily.* If edema develops despite this precaution, the cautious use of diuretics may be necessary.

Hypopotassemia. High dosage of CORTONE has caused increased urinary excretion of potassium and chloride, with metabolic alkalosis in a few patients In such cases, potassium depletion resulting from the electrolyte loss has produced symptoms of weakness, electrocardiographic changes characteristic of hypopotassemia (such as lowering of T-waves and depression of the S-T segment and the S-T junction), and hypotension.

Hypopotassemia can be detected early and avoided by paying careful attention to the CO_2 combining power, the electrocardiogram, and the blood chloride level, and usually

Prolonged administration of large doses of CORTONE in animals causes reduction in the size of the adrenal cortex. In humans, adrenal cortical suppression with muscular weakness and asthenia has been observed to occur temporarily after treatment was withdrawn abruptly. This suggests that a transient period of adrenal cortical insufficiency may exist after prolonged administration of CORTONE is discontinued. Return of adrenal function may be expected within two to four weeks, rarely longer. In certain patients a temporary reduction of urinary corticosteroids and 17-ketosteroids has been observed, as well as a *temporary hypoglycemia in rare instances, and occasional* suppression of eosinophil response.

Mental Changes: An increase of approximately 10 per cent in the frequency of alpha waves, or a reduction in their amplitude, has been observed in the electroencephalograms of some individuals In other instances, it appears that abnormal, slow rhythms may be produced by CORTONE. The abnormal electroencephalographic findings in patients with Addison's disease are restored to normal.

Certain mental changes have been reported. The usual psychic response to CORTONE is a desirable increase in the sense of well-being, often with acceleration of the alpha waves of the electroencephalogram However, an occasional individual may develop pronounced psychic derangement, sometimes early during the course of therapy, but more especially if high dosage has been used for protracted periods In certain instances, the increase in psychomotor activity temporarily produces an exaggerated sense of well-being and, infrequently, a manic state. Conversely, mental depression has been reported in a few cases. Insomnia has been noted in many individuals. In *rare instances, pre-existent or latent mental derangement,* such as schizophrenia, seems to be intensified or precipi-

discontinuance. When a patient with diabetes mellitus is treated for a concurrent disease amenable to CORTONE, the diabetic status must be followed and regulated with great care. It usually is not difficult to compensate for the anti-insulin effect of CORTONE by administering larger doses of insulin. (Cases have been reported where two or more times the usual requirement were needed.)

In nondiabetic patients, CORTONE may sometimes induce transient renal glycosuria or hyperglycemia with glycosuria. In all such cases thus far reported, these temporary changes have disappeared soon after administration of CORTONE was discontinued, with no permanent ill effects. It is of interest that cases of mild or latent diabetes may be discovered during treatment with CORTONE.

Protein Metabolism is affected in many patients, especially those receiving high dosage of CORTONE. Continued administration of large doses usually produces a negative nitrogen balance. This may be overcome in most instances by increasing the food intake (especially protein), with or without the administration of testosterone. Where reversed albumin-globulin ratios are present, these tend to revert toward normal. Creatine and uric acid excretion are increased, and changes occur in the pattern of amino acid excretion.

General Hormonal Effects

With prolonged high dosage, and in certain patients on the usual therapeutic dose, unwanted hormonal effects may occur.

In some cases, the hormone has produced evidences of excessive adrenal cortical effect such as rounding of the face, mild hirsutism, acne, striae of the skin, and in a few instances, amenorrhea. All significant phenomena disappeared after administration was discontinued.

insufficiency. This also applies to the management of any patient who has been confined to bed for protracted periods of time.

Masking of Infection During Therapy with CORTONE

Signs and symptoms of acute or active chronic infection may be obscured during therapy with CORTONE, also, this hormone may tend to activate latent infections.

Particular caution is necessary with regard to avoiding activation or spread of tuberculosis. Every patient who is to be treated with CORTONE for any considerable length of time, *e. g.*, in rheumatoid arthritis, should have a chest X-ray. Even in the presence of presumably healed tuberculous lesions, CORTONE should be administered with great caution and the status of pulmonary lesions observed with X-ray and other methods of rechecking repeated at appropriate intervals. (Patients with previously positive tuberculin tests may fail to show a skin reaction while receiving CORTONE.)

Supervision of Patient Following Therapy

Continued supervision of the patient after discontinuance of CORTONE is essential, because this substance may continue to show its effects for some time after the last dose. There may be a sudden reappearance of severe manifestations of the disease for which the patient was treated, or delayed evidence of infection, psychotic episodes, and the like, may appear. It should be noted, however, that the effect of CORTONE administered orally wears off after eight to fourteen hours. Abrupt withdrawal of CORTONE should be avoided whenever possible

tated. In such cases, premonitory symptoms of the psychotic reaction usually occur, such as pronounced insomnia and exaggerated swings of mood. Prompt reduction of dosage at this point usually suffices to avoid the development of actual psychotic episodes. Abrupt withdrawal usually is best avoided unless the psychotic symptoms already are severe.

Effect on Wound Healing: Animal experiments, using large doses of CORTONE, have shown delay in wound healing, however, this has not been found to be of practical importance in humans receiving therapeutic doses of CORTONE. Primary healing of skin wounds seldom is affected by usual-size therapeutic doses.

Blood Pressure: Although moderate elevation of blood pressure may occur, significant increases are rare. The latter possibility, however, does exist in patients in whom antecedent vascular or renal damage is present, especially the latter, and when sodium and water retention develops. In patients with essential hypertension, the resting blood pressure occasionally may be decreased.

Prothrombin Time: In some cases, decrease in prothrombin time has been noted, and there may be an increase in tendency to develop thromboembolic phenomena. This also has been reported on cessation of treatment or abrupt reduction in dosage.

Prevention of Overexertion

As mentioned previously, patients receiving CORTONE frequently experience a pronounced sense of well-being, which is usually accompanied by increased psychomotor activity. Therefore, it is advisable to restrict the activity of patients who have cardiovascular disease, such as coronary

mechanism of the action of CORTONE against disease processes. This widespread co-operative research effort may be expected to bring about a new concept of the nature of many diseases.

It seems likely that the therapeutic action of CORTONE involves not only the many known physiologic properties of the hormone, but also various thus far undiscovered effects on the chemical processes of organs, tissues, and cells of both the normal and the diseased organism In any event, it has not yet been demonstrated that the mode of action of CORTONE can be attributed to a single, circumscribed mechanism. However, in the TABLE on pages 116–117 will be found listed those effects on which there presently is general agreement.

Among the readily demonstrable physiologic properties of CORTONE are its strong effect on the metabolism of carbohydrate and protein, and its rather mild influence on the metabolism of water and electrolytes. In altering the metabolism of two of the chief sources of energy—protein and carbohydrate—CORTONE also modifies the metabolism of fat.

Another important function of CORTONE appears to be that of increasing the resistance of the organism to certain forms of stress, such as exposure to cold, starvation, and physical exertion. Whether the metabolic effects of the hormone are part of the mechanism of this increased resistance, or are merely coincidental to it, has not been established.

Physiologic Considerations

The precise interrelationships of the adrenals, the pituitary, and the various tissues of the body are not clearly defined. Moreover, the functions and modes of interplay of the individual steroid hormones produced by the adrenal cortex are extremely complex.

The Pituitary-Adrenal Relationship

The present concept, as outlined in the schematic drawing on *Plate XXXI*, is that the secretion of cortisone and other cortical steroid hormones is mainly or entirely mediated through stimulation of the adrenal cortex by the adrenocorticotropic hormone; this hormone is elaborated by the anterior pituitary. The function of the anterior pituitary is presumably controlled to some degree by the hypothalamus which, in turn, can be influenced by higher brain centers. The adrenocorticotropic hormone has the specific function of regulating the activity of the adrenal cortex. It is in response to the action of this hormone that the adrenal cortex secretes its steroid hormones.

The direct or indirect humoral pathway between the hypothalamus and anterior pituitary is only one of the ways in which the gland is stimulated to produce adrenocorticotropic hormone. Another regulatory mechanism involves the adrenal medulla which, in response to stress, releases epinephrine. However, this effect thus far has not been found of practical value from the standpoint of therapeusis.

Principal Effects of CORTONE

During the past few years, much valuable and intensive work has been directed toward clarifying the fundamental

Effects of CORTONE

IMMUNOLOGIC & SEROLOGIC	CYTOLOGIC	ENZYMOLOGIC
Tends to bring [illegible]	Produces lympho- [illegible]	Diminishes hyalu- [illegible]
Diminishes anti-body response under certain experimental conditions in animals.	May increase tissue eosinophils.	of mice.
Diminishes or abolishes [illegible]	Stimulates reticu- [illegible] [illegible]action [illegible]	Increases urinary excretion of uropepsin in patients with Addison's disease.

Known (or Probable)

METABOLIC	INTERENDOCRINE	NEUROMUSCULAR
Increases gluconeogenesis. Lowers renal threshold for glucose. Opposes the action of insulin. Increases absorption and storage of fat. Increases catabolism creases its lism; in urinary creatine, acid Increases tion of glycogen.	Depresses corticotropin output by anterior pituitary; causes morphologic involution of adrenal cortex (except zona glomerulosa). May depress thyroid activity Increases insulin requirement. In in	Partly restores capacity of muscle for work in adrenalectomized animals. May increase muscle strength (in rheumatoid arthritis) or may cause muscle weakness, at least in some cases, as a *result*
May bring about retention of sodium. Increases urinary excretion of chloride and potassium. May increase calcium and phosphorus excretion.	May restore normal diuretic response to ingested water in Addison's disease. Hypoglycemia may occur following withdrawal of CORTONE. May delay or inhibit menstruation.	May restore electroencephalographic pattern to normal in Addison's disease. May induce exaggerated sense of well-being and increased psychomotor activity. May precipitate psychotic reaction (probably only in predisposed individuals).

Effects of CORTONE

IMMUNOLOGIC & SEROLOGIC	CYTOLOGIC	ENZYMOLOGIC
Tends to bring	Produces lympho-	Diminishes hyalu-
in animals	Stimulates reticulocyte production or release.	pepsin in patients with Addison's disease
Diminishes or abolishes tuberculin reaction (when given in high dosage).	May increase neutrophils in peripheral blood.	
May prevent vascular lesions otherwise resulting from injection of desoxycorticosterone (rats) or heterologous serum (rabbits).	Inhibits fibroplasia. In heavy dosage may occasionally retard wound healing and may reactivate chronic ulcers (e g., peptic ulcer).	
Prevents or reduces tissue reaction to chemical irritants	Increases growth of macrophages in tissue culture.	
cemia following infection		
May suppress signs and symptoms of infection.		

Research and Development

The combined work culminating in the chemical synthesis of cortisone and its introduction into clinical medicine is one of the epics of modern medical research. In recognition of their decisive contributions to this far-reaching advance, Dr. Philip S. Hench, of the Mayo Clinic, and Dr. Edward C. Kendall, of the Mayo Foundation, were jointly awarded the *1950 Nobel Prize for Medicine*, together with Prof. Tadeus Reichstein, of Basle, Switzerland.

EXTENT OF THE RESEARCH

Of all the endocrine glands, the adrenal cortex is among the last to yield its secrets to the investigator. Two decades of intensive investigation were required from the time when the physiologic activity of the adrenal cortex was first decisively demonstrated until cortisone could be made available for use in clinical medicine. This is a measure of the unprecedented difficulties that had to be surmounted.

Though the importance of the adrenal gland long had been recognized, the adrenal cortex itself was for many years largely neglected by investigators It was not until 1930, when Swingle and Pfiffner prepared an extract of the adrenal cortex capable of maintaining life in adrenalectomized animals, that increasing attention was directed to studies of this part of the gland. Further investigations demonstrated that several hormonal compounds were present in cortical extracts. It was then that chemical investigations were first directed toward attempted isolation and synthesis of the active principles. *Investigations of the* [illegible] *during the decade of 1930–1940*

of no less than twenty-eight crystalline compounds. When tested in small animals, four of these showed significant physiologic activity. These compounds, designated by the letters A, B, E, and F in Kendall's laboratory, were what came to be known as 11-dehydrocorticosterone, corticosterone, 11-dehydro-17-hydroxycorticosterone, and 17-hydroxycorticosterone. Later, Compound E was named cortisone by Dr. Kendall.

Little was known at that time about the relative value of the newly discovered cortical hormones, and the only way to determine this was to make them available in quantities sufficient for the necessary clinical trials. For a time it was thought that 11-dehydrocorticosterone (Kendall's compound A) showed promise. But to obtain a quantity of this compound, the size of one small tablet required half a ton of adrenal glands from cattle. The supply of beef adrenal glands was necessarily limited by the number of cattle killed, and the quantities of these compounds that could be obtained in the laboratory were therefore insignificant.

SYNTHESIS OF COMPOUND A

The only hope was to discover some means of producing the compounds by chemical synthesis. As with so many other difficult scientific problems, World War II provided a major stimulus to the efforts at synthesis and large-scale production of adrenal cortical hormones It was thought that these hormones or closely related substances might be of value in aviation medicine and in the treatment of shock and battle fatigue There were rumors that Germany was acquiring the adrenal output of the Argentine slaughterhouses, extracting these glands, and administering the extracts to *Luftwaffe* pilots. According to these rumors, the adrenal extracts enabled the pilots to fly and fight at altitudes of forty thousand feet without difficulty. Though

untrue, the rumors persisted, and provided a real impetus to attempts to synthesize adrenal cortical hormones.

In 1941, the National Research Council placed the subject of adrenal cortical hormones at the top of its war research agenda—along with penicillin and antimalarial agents. By the time of the attack on Pearl Harbor, Dr. Kendall was able to report progress in his studies to Research Corporation and to the wartime Committee on Medical Research of the Office of Scientific Research and Development. The committee informed Dr. Kendall and Research Corporation that the Government considered research on adrenal hormones to be a project of national importance. Accordingly, to help further Dr. Kendall's work, Research Corporation and Dr. Kendall enlisted the aid of Merck & Co., Inc.

Shortly thereafter, the National Research Council called an official conference in Washington, D. C., inviting scientific representatives of the Mayo Clinic, certain universities, and a few industrial organizations, including Merck & Co., Inc., to survey possible production of adrenal cortical hormones. Merck already had sent one of its senior chemists to the Mayo Clinic for a period of consultation, at the invitation of Dr. Kendall and Research Corporation.

Under this co-operative arrangement, important chemical intermediates were prepared in the Merck Laboratories and supplied to Dr. Kendall, who, in 1944, succeeded in synthesizing compound A. However, this compound proved to have little physiologic activity in the treatment of shock, fatigue, and related conditions, and for such war purposes its investigation was apparently fruitless.

CLINICAL OBSERVATIONS

In the meantime, Dr. Hench[2] had made certain observations during the course of his studies on rheumatoid arthritis which indicated to him that an adrenal cortical hormone

might prove effective in reversing the disease. It was his reasoning that "Within every rheumatoid patient corrective forces lie dormant, awaiting proper stimulation. Therefore, the disease is not necessarily a relentless condition for which no satisfactory control should be expected. The inherent reversibility of rheumatoid arthritis is activated more effectively by the intercurrence of jaundice or pregnancy than by any other condition or agent thus far known. Regardless of the supposed validity of the microbe theory [in arthritis], rheumatoid arthritis can be profoundly influenced by phenomena which are primarily biochemical."

This belief was strengthened by his recognition that temporary remissions of rheumatoid arthritis also are often brought about by procedures that now are known to stimulate the adrenal cortex, such as surgical operations or general anesthesia Following one of his many conferences with Dr. Kendall on this subject, Dr. Hench made this entry in his notebook, in January 1941: "Try compound E in rheumatoid arthritis." But more than seven years were to elapse before he was able to do so.

SYNTHESIS OF CORTONE

As yet, there was no conclusive evidence that compound E (cortisone) would be qualitatively different from compound A. Therefore, there was no assurance that large-scale production of the compound would be worthwhile. Nevertheless, Merck & Co., Inc. decided to proceed in an

PROCESS IMPROVEMENTS

During the following eighteen months, important improvements of the original *test-tube synthesis* were devised through continuing co-operation between Dr. Kendall at the Mayo Foundation and the Merck staff of development chemists. It was due to the skilled operations of this team that, by 1948, the hormone could be produced in amounts sufficient for clinical trial.

THE FIRST CLINICAL TRIALS

When, in September 1948, Dr. Hench learned that a small amount of the compound had been produced, he requested a supply from Merck & Co., Inc. for clinical trial. In making this request, Dr. Hench expressed the belief that if it were to prove effective, "we would expect to see some results in a very few days" A small supply of the compound was sent to Dr. Hench and on September 21, 1948, 100 mg. were first injected into a patient with rheumatoid arthritis. Throughout the Winter of 1948-1949, fifteen more arthritic patients received the hormone, and in the Spring, five patients with acute rheumatic fever were treated. Profoundly beneficial effects were observed in every patient. With these pioneering studies, a new concept of the nature and treatment of disease was born.

RECENT PROGRESS

Since then, the field of usefulness for CORTONE has [illegible] tremendously to include not only arthritic con- [illegible] diseases, allergies, and [illegible]

The methods for synthesizing and producing CORTONE have improved remarkably, and today the medical profession is assured of a continuing supply. The addition of new dosage forms, for oral and ophthalmic use, has made CORTONE not only a strikingly effective, but also a highly

practical agent for the individualized treatment of ambulatory patients.

Development of HYDROCORTONE

(HYDROCORTISONE of MERCK & CO., INC.)
(17-hydroxycorticosterone)

The recent development of HYDROCORTONE (Hydrocortisone of Merck & Co., Inc.) and its clinical trial mark the introduction of another important hormone into clinical medicine

Early in 1950, the Merck research team of N. L. Wendler, R. P. Graber, R. E Jones, and M. Tishler[4] synthesized Kendall's Compound F (hydrocortisone) from an intermediate compound obtained in Sarett's procedure for synthesizing cortisone

Shortly thereafter, Thorn[5] injected the new material directly into a rheumatoid arthritic knee. He noted prompt alleviation of the inflamed joint, but since this was coincident with a general improvement in the condition of the patient, it was thought that the action was systemic and no further experiments were conducted

Several months later, the theory of local injection received re-evaluation, but this time with CORTONE. Hollander, Brown, and Stoner[6] attempted local therapy by injecting 25 mg of CORTONE suspension directly into the inflamed knee joints of seven patients with rheumatoid arthritis However, their results were not comparable with those obtained by systemic dosage, and despite their observation that locally injected CORTONE had some beneficial action in three of the patients, the team concluded that the action was too transient and of insufficient degree to be of practical value.

Freyberg, *et al.*,[7] injected 50 mg. of CORTONE, also locally, into rheumatoid arthritic knee joints Although the benefits now seemed more consistent, again the effects were

too transient and inadequate to be of practical value in most cases.

Finally, the hypothesis was advanced that *at the tissue level* hydrocortisone rather than cortisone might be the principal corticoid with anti-inflammatory activity. When HYDROCORTONE Acetate became available in January 1951, it was decided to attempt local administration of the hormone and to compare its effect with that of CORTONE in the rheumatoid arthritic joint.[6]

Injected locally into one or more joints, HYDROCORTONE Acetate was seen to be strikingly effective in suppressing the *synovial inflammation of rheumatoid arthritis.* Furthermore, the favorable results were highly consistent, and without untoward effects. In osteoarthritis, treatment with HYDROCORTONE Acetate was followed by relief of pain, swelling, and tenderness, and function of the involved joint was resumed. The precise mechanism through which HYDROCORTONE acts has not been fully described as yet.

The dramatic action of HYDROCORTONE in rheumatoid arthritis and osteoarthritis has encouraged its experimental use in various forms of bursitis, gouty i-
nated lupus erythematosus, traumatic arth
lar inflammations, complicating rheumatoi
high rate of efficacy and safety
HYDROCORTONE indicates that the
an important position in the physician'

REFERENCES

[1] Pfiffner, J. J, Wintersteiner, O, and Vars, H. M.: *J. Biol. Chem.* **111:** 585, November 1935; Wintersteiner, O., Pfiffner, J. J.: *ibid.* **116:** 291, November 1936; Mason, H. L., Myers, C. S, Kendall, E C.: *ibid* **114:** 613, July 1936; Reichstein, T: *Helv. Chim Acta.* **19:** 1107, October 1936.

[2] Hench, P. S., Kendall, E. C, Slocumb, C. H, Polley, H. F.: *Proc. Staff Meetings, Mayo Clin.* **24:** 181–197, April 13, 1949.

[3] Sarett, L. H.: *J Biol Chem.* **162:** 601, March 1946; *J Am Chem. Soc* **70:** 1454, April 1948.

[4] Wendler, N. L., Graber, R. P., Jones, R. E, and Tischler, M.: *J. Am Chem Soc* **72:** 5793, December 1950

[5] Thorn, G. W Personal Communication.

[6] Hollander, J L, Brown, E M, Jr, and Stoner, E. K.: Unpublished data.

[7] Freyberg, R H, Patterson, M, Adams, C. H., Durivage, J., and Traeger, C H.. *Ann Rheumat Dis.* **10:** 1–13, March 1951.

[8] Hollander, J. L., Brown, E M, Jr., Jessar, R. A, and Brown, C. Y. *J.A.M.A* **147:** 1629–1635, December 22, 1951

too transient and inadequate to be of practical value in most cases.

Finally, the hypothesis was advanced that *at the tissue level* hydrocortisone rather than cortisone might be the principal corticoid with anti-inflammatory activity. When HYDROCORTONE Acetate became available in January 1951, it was decided to attempt local administration of the hormone and to compare its effect with that of CORTONE in the rheumatoid arthritic joint.[8]

Injected locally into one or more joints, HYDROCORTONE Acetate was seen to be strikingly effective in suppressing the synovial inflammation of rheumatoid arthritis. Furthermore, the favorable results were highly consistent, and without untoward effects In osteoarthritis, treatment with HYDROCORTONE Acetate was followed by relief of pain, swelling, and tenderness, and function of the involved joint was resumed. The precise mechanism through which HYDROCORTONE acts has not been fully described as yet.

The dramatic action of HYDROCORTONE in rheumatoid arthritis and osteoarthritis has encouraged its experimental use in various forms of bursitis, gouty arthritis, disseminated lupus erythematosus, traumatic arthritis, and ocular inflammations, complicating rheumatoid arthritis. The high rate of efficacy and safety attending the use of HYDROCORTONE indicates that the hormone will receive an important position in the physician's armamentarium

INDEX

CORTONE ACETATE

(Cortisone Acetate of Merck & Co., Inc.)

Oral:

CORTONE Acetate Tablets
25 mg. each, bottles of 20 tablets
25 mg. each, bottles of 40 tablets
5 mg. each, bottles of 50 tablets

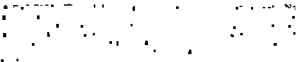
Parenteral

SALINE SUSPENSION OF CORTONE ACETATE
(for intramuscular use)
Each cc. = 25 mg., vials of 20 cc.
Each cc. = 50 mg., vials of 10 cc.

Topical (Ophthalmic):

OPHTHALMIC SUSPENSION OF CORTONE ACETATE
(in two concentrations)*
0.5% — 5-cc. vials
2.5% — 5-cc. vials

OPHTHALMIC OINTMENT OF CORTONE ACETATE
1.5% — ⅛-oz. tubes



HYDROCORTONE

(Hydrocortisone of Merck & Co., Inc.)

Intra-Articular Injection

SALINE SUSPENSION OF HYDROCORTONE ACETATE†
25 mg. per cc., vials of 5 cc. each

Oral:

HYDROCORTONE Tablets
20 mg. each, bottles of 25 tablets

PRODUCT INFORMATION

CORTONE ACETATE

(Cortisone Acetate of Merck & Co., Inc)

Oral·

CORTONE Acetate Tablets

25 mg. each, bottles of 20 tablets
25 mg. each, bottles of 40 tablets
5 mg. each, bottles of 50 tablets

Parenteral

SALINE SUSPENSION OF CORTONE ACETATE
(for intramuscular use)

Each cc. = 25 mg, vials of 20 cc.
Each cc = 50 mg, vials of 10 cc

Topical (Ophthalmic)

OPHTHALMIC SUSPENSION OF CORTONE ACETATE
(in two concentrations)*

0 5% — 5-cc vials
2.5% — 5-cc vials

OPHTHALMIC OINTMENT OF CORTONE ACETATE

1 5% — ⅛-oz tubes

* *CAUTION* The ophthalmic suspensions are for topical use only No

HYDROCORTONE

(Hydrocortisone of Merck & Co., Inc)

Intra-Articular Injection

SALINE SUSPENSION OF HYDROCORTONE ACETATE†

25 mg per cc, vials of 5 cc each

Oral

HYDROCORTONE Tablets

20 mg each, bottles of 25 tablets